Dossier for *Valtrex*

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This information is provided in response to your request for information about *Valtrex*® (valacyclovir hydrochloride).

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This response was developed according to the principles of evidence-based medicine and, therefore, references may not be all-inclusive.

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1. Change Summary

The Pivotal Efficacy and Safety section was updated with the clinical information for the recent indication for chickenpox in children 2< 18 years of age.

2. EXECUTIVE SUMMARY

Overview

Valtrex is the hydrochloride salt of the L valyl ester antiviral drug acyclovir. Valacyclovir hydrochloride is rapidly converted to acyclovir which has demonstrated antiviral activity against herpes simplex virus types 1 (HSV 1) and 2 (HSV 2) and varicella zoster virus (VZV) both *in vitro* and in vivo.(1)

The addition of the L-valyl ester to acyclovir results in 3-5 times higher bioavailability of *Valtrex* than that observed with acyclovir. Due to this improved bioavailability, *Valtrex* provides higher antiviral serum concentrations and less frequent dosing than acyclovir. Since valacyclovir is rapidly and nearly completely (99%) converted to acyclovir, *Valtrex* shares the same spectrum of in vitro antiviral activity as acyclovir. (1)

Valtrex is indicated for the episodic and suppressive treatment of recurrent genital herpes, the reduction in the risk of transmission of genital herpes in heterosexual adults when used as suppressive therapy in combination with safer sex practices, the treatment of initial genital herpes, the treatment of herpes zoster, and the treatment of cold sores in immunocompetent adults. *Valtrex* is also indicated for the suppression of genital herpes in HIV-infected patients.(1)

sumMary of key clinical studies with *valtrex*

Initial Genital Herpes

Valtrex is approved for the treatment of first episode (true primary and non-primary) genital herpes at a dose of 1 g PO (orally) BID (twice daily) for 10 days. In a large, randomized, double-blind clinical trial, *Valtrex* 1 g PO BID for 10 days and acyclovir 200 mg PO five times daily for 10 days were equally effective in reducing the duration of viral shedding, time to complete cessation of pain and promoting the complete healing of lesions in patients with initial genital herpes infections.(1)

Short-Course Episodic Therapy of Recurrent Genital Herpes

Valtrex is approved for the treatment of recurrent episodes of genital herpes with a three-day treatment regimen (500 mg BID for three days). The results of a randomized, double-blind, multicenter trial have shown that three and five-day courses of therapy with *Valtrex* 500 mg BID for the episodic treatment of genital herpes infections are equivalent in terms of median time to lesion healing, median duration of pain, median length of episode and proportion of patients with aborted (non-progressing) lesions. (1,2)

Suppressive Therapy with Valtrex For Genital Herpes

Valtrex is the only oral antiviral approved for once daily dosing for the suppression of genital herpes outbreaks. The recommended dosage of *Valtrex* for suppressive therapy of recurrent genital herpes is 1 gram QD (once daily). In patients with a history of 9 or fewer recurrences per year, an alternative dose is 500 mg QD.(1)

In a large, placebo-controlled trial, 34% of patients were recurrence-free at 12 months with once daily *Valtrex* 1 g, 31% were recurrence-free on once daily *Valtrex* 500 mg, and 4% of patients were recurrence free on placebo. The median time to first recurrence was 337 days for patients receiving *Valtrex* 1 g QD versus 31 days for patients receiving placebo. In patients with 9 or fewer recurrences per year, the median time to first recurrence was 309 days for patients receiving *Valtrex* 500 mg QD versus 30 days for patients receiving placebo. (1,3)

A randomized, double-blind study compared famciclovir 250 mg BID and *Valtrex* 500 mg QD for the suppression of recurrent genital herpes in patients (n=320) with a history of ≥ 6 recurrences per year. The proportion of patients with a clinically confirmed recurrence of genital herpes was similar in both groups (famciclovir 34%, valacyclovir 28%; *P*=0.22). Time to first clinically-confirmed recurrence was similar between groups.

Reduction In The Risk of Sexual Transmission of Genital Herpes

Valtrex is the only antiviral approved for the reduction in the risk of heterosexual transmission of genital herpes in immunocompetent adults when used as suppressive therapy in combination with safer sex practices.(1)

Valtrex was evaluated in a multicenter, randomized, double-blind, placebo-controlled study for the reduction in the risk of transmission of HSV-2 genital herpes in healthy heterosexual monogamous couples (n=1484) discordant for the presence of HSV-2 antibody. [1,4] HSV-2 source partners with a history of 9 or fewer genital herpes outbreaks per year were randomized to either *Valtrex* 500 mg QD or placebo for 8 months. Couples were offered condoms and counseled on safer sexual behavior throughout the study.

For the primary endpoint, the proportion of couples with symptomatic genital HSV-2 infection in the susceptible partner was 2.2% (16/741) in the placebo group and 0.5% (4/743) in the group receiving *Valtrex* (*P*=0.011, a reduction of 75%). [4]

Proportion of couples with overall acquisition of genital HSV-2 infection in the susceptible partner was 3.6% (27/741) in the placebo group and 1.9% (14/743) in the group receiving *Valtrex* (*P*=0.054, a reduction of 48%). Time to overall acquisition was significantly shorter in the placebo group compared to the group receiving *Valtrex* (*P*=0.039). [4]

Herpes Zoster

Valtrex is approved for the treatment of herpes zoster at a dose of 1 gram three times daily (TID) for 7 days. [1]

In a large, well-controlled clinical trial, *Valtrex* was more effective than oral acyclovir in the treatment of zoster associated pain (ZAP) and postherpetic neuralgia (PHN) in patients ≥50 years of age. In this study the median duration of pain, defined as either ZAP or PHN, was significantly shorter for patients receiving *Valtrex* 1 g three times daily for 7 days compared with patients receiving acyclovir 800 mg PO five times daily for 7 days. A subset analysis of this data was performed and is the basis for the data found in the current *Valtrex* . [1] Median duration of pain after rash healing was 40 days in the *Valtrex* recipients and 59 days in patients receiving acyclovir, *P*=0.06.

A randomized, double-blind study compared *Valtrex* 1 g three times daily for 7 days to famciclovir 500 mg three times daily for 7 days in 597 immunocompetent patients. Results indicated no difference in any parameter tested including PHN, ZAP, duration of abnormal sensations, time to rash healing, or safety profile.[1,5]

In a placebo-controlled trial evaluating the safety and efficacy of *Valtrex* for the treatment of herpes zoster in immunocompetent patients <50 years of age, *Valtrex* reduced the median time to cessation of new lesion formation from 3 days with placebo to 2 days with *Valtrex*. No difference was found with respect to post-herpetic neuralgia.

Use of Valtrex for the Management of Cold Sores (Herpes Labialis)

Valtrex is the only oral antiviral approved for the treatment of cold sores (herpes labialis) with a one-day treatment regimen in immunocompetent adults at a dose of 2 g BID for 1 day. Based on a combined analysis of two double-blind, randomized, placebo-controlled studies which included 1,856 otherwise healthy patients with recurrent cold sores, *Valtrex* 2 g BID for 1 day showed significant improvement in time to lesion healing, time to cessation of pain/discomfort and time to complete resolution of outbreak as compared to placebo.

Suppression of Genital Herpes in HIV-infected Patients

Valtrex is the only oral antiviral approved for the suppression of genital herpes in HIV-infected patients at a dose of 500 mg BID. *Valtrex* was evaluated in a multicenter, randomized, double-blind, placebo-controlled study for the suppression of recurrent ano-genital HSV infections in HIV-infected individuals (n =293). The proportion of patients recurrence free of ano-genital HSV at 6 months was significantly higher in patients receiving *Valtrex* compared with placebo (65% vs. 26%, p<0.001). The time to first ano-genital HSV recurrence was significantly shorter in the placebo group compared to the group receiving *Valtrex* (P<0.001).

safety

In immunocompetent adults, commonly reported adverse events with *Valtrex* include nausea, headache, vomiting, abdominal pain, and dizziness. For HIV-infected patients receiving suppressive therapy with *Valtrex*, commonly reported adverse events included headache, fatigue and rash. [1]

Dosage reduction is recommended when administering *Valtrex* to patients with renal impairment. Please refer to the recommended dosing adjustments in the Prescribing Information for *Valtrex*. (1)

Thrombotic thrombocytopenia purpura/hemolytic uremic syndrome (TTP/HUS), in some cases resulting in death, has occurred in patients with advanced HIV disease and also in allogeneic bone marrow transplant and renal transplant recipients participating in clinical trials of *Valtrex* at doses of 8 grams per day. (1)

3. DISEASE DESCRIPTION

3.1 Disease Descripton Of Herpes Labialis (Cold Sores)

Herpes Labialis: epidemiology

Herpes labialis is the most prevalent recurrent infection caused by herpes simplex virus type 1 (HSV-1). Greater than 150 million people in the United States are infected with HSV 1.(6) Of the United States population 50 years of age and older, 80%-90% are seropositive for HSV-1 and 20-40% of those patients experience recurrent outbreaks.(7) Approximately 30-60% of children under ten years of age are exposed to HSV-1 through intimate contact with someone who has the virus.

Herpes Labialis: pathophysiology

Initial infection with HSV-1 is often asymptomatic; however it may present with symptoms in some patients. Following initial infection with HSV-1 the virus establishes a chronic, latent infection in the nerve ganglia and subsequently will recur at varying intervals throughout the person's lifetime.(7) Upon reactivation, the virus travels to the peripheral epithelium and replicates to manifest as a cold sore. Within 2-3 cycles of viral replication, a clinically apparent cold sore lesion can form. Most individuals who experience recurrences have 3 or 4 per year. (8) Although uncommon, patients can have recurrences monthly or at more frequent intervals.

Herpes Labialis: clinical presentation

Recurrent herpes labialis is often preceded by prodromal symptoms which include pain, tingling or itching. These symptoms may last up to 6 hours with occasional symptoms lasting up to 24 48 hours. (9) Lesion outbreaks occur in 90% of patients who experience the prodromal stage.(10) Painful fluid-filled vesicles (cold sores, fever blisters) commonly appear on the vermilion border of the lip within 12 hours of the first indication of skin induration or papule. These vesicles rupture rapidly and form nondescriptive ulcers. The time course for lesions to progress from the vesicle to the ulcer/crust stage is approximately 48 hours.(7) Vesicle-associated pain is most severe within the first 24 hours after the initial appearance of the lesions.(7) The healing process usually is complete within 810 days.

Herpes Labialis: place in therapy/goal of therapy

Valtrex is FDA-approved for the treatment of cold sores in immunocompetent adults. *Valtrex* has been proven to shorten the duration of a cold sore outbreak.(1) Treatment should be initiated at the earliest symptom of a cold sore (tingling, itching, or burning). Based on a combined analysis of two double-blind, randomized, placebo-controlled studies which including 1,856 patients, *Valtrex* showed significant improvement in lesion healing, time to cessation of pain/discomfort and time to complete resolution of outbreak as compared to placebo. (11)

3.2 Disease Description of Genital Herpes

Genital herpes: epidemiology

it is estimated that one in five Americans >14 years of age (50 million) are infected with herpes simplex virus type 2 (HSV-2).(12) The CDC estimates that approximately 1 million new cases of genital herpes infections occur each year.(12) The majority of people infected with herpes simplex virus (HSV) are unaware that they have genital herpes either because they have symptoms but do not recognize them, or they have asymptomatic infection.(12) According to a recent study of 36 primary care physician (PCP) offices in relatively affluent suburban areas of six U.S. cities, one-fourth of people (25.5 percent) tested positive for the virus that causes genital herpes, despite the fact only four percent reported a history of genital herpes. (13) As the study shows, genital herpes infection rates were high even among suburban,

educated and mid-high income populations. [13] Clinical studies have shown that among couples discordant for HSV-2, the rate of transmission may be in the order of 3.5-10% per year. [14] [15] [16] [17] In these studies, patients were counseled on safer sex practices, including the use of condoms. Risk factors for transmission involve both biological and behavioral characteristics. Persons at a higher risk for acquiring genital herpes include females, those with frequent sexual activity and those with increased number of sexual partners. [15] [18]

Genital Herpes: Pathophysiology

The predominant viral pathogen for genital herpes HSV-2, although more and more cases of genital herpes are being caused by HSV-1. The mode of transmission is via either genital or oral-genital sexual contact.[19] The incubation period after sexual contact ranges from 1 –14 days, but symptoms usually occur within 3-7 days after exposure.

[20]

Following primary infection, either the intact viron or the capsid is transported via neurons to the dorsal root ganglia where latency is established. During reactivation, the virus travels back to mucosal surfaces where it replicates. These reactivations can be either symptomatic or asymptomatic. In symptomatic reactivations patients experience lesions which are often preceded by a prodromal symptoms. During asymptomatic reactivations, patients experience viral shedding when no visible lesions are present.

Recurrence rates vary by individual, by type of herpesvirus, location of herpesvirus and immune function. In general, genital infections caused by HSV-1 are less severe and recurrences are less frequent than genital infections caused by HSV-2. [21] Almost 90% of patients with first-episode HSV-2 infection will have a recurrence within 12 months compared to 60% of those with primary HSV-1 infections. [22] [23] The median recurrence rate for genital HSV-2 in the first year of infection has been reported to be 4-6, decreasing to 4 recurrences/year during the second year. [23] [24] While the overall recurrence rates for genital HSV-1 in the first year of infection have been reported to be 1.3/year, decreasing to 0.7/year in the second year. [21] Recurrence rates generally decrease in the years following a primary infection. However, the rate of this decline is highly variable.[24] In HSV-2 seropositive patients who were followed for at least 4 years, there was a median decrease of 2 recurrences over this time period. However, 25% of the patients followed for at least 4 years had an increase of at least one recurrence in year five. [24] For patients who are seropositive for HSV-1 and subsequently experience a first episode of genital herpes caused by HSV-2 (nonprimary infection), the manifestations of the outbreak are typically associated with less frequent systemic symptoms, decreased pain, and faster healing than primary genital infection with HSV-2.[25]

Genital herpes symptoms do not have to be present to infect another individual. In fact, one study showed that up to 70% of genital herpes may be spread by people who are asymptomatically shedding virus. [15] Asymptomatic viral shedding (shedding in the absence of lesions) can be identified from many anatomical sites and various body fluids in the absence of genital lesions in both men and women. Most patients with genital herpes experience asymptomatic shedding, which often occurs independent from an outbreak. [26] [27] Asymptomatic shedding occurs following genital infections with both HSV-2 and HSV-1. However, the overall rate of genital shedding is less for HSV-1 than for HSV-2.[27]

Genital Herpes: Clinical presentation

Primary infection with genital herpes is characterized by ulcerative genital lesions that evolve into pustules and crust within several days. New lesions may continue to form for a week or longer. The lesions may coalesce and form large areas that look like burns. Vaginal mucosa, the vulva and often the cervix are involved with an associated watery vaginal discharge. Other symptoms include burning, tenderness, vulvar pain, dysuria, erythema, fever, myalgia, headache and malaise.[19] These symptoms usually peak in 8-10 days. Viral shedding may occur for up to several weeks after the initial episode, and is generally attributed to continued activity at the cervix, even though external lesions have healed.

Recurrent disease typically does not produce the systemic symptoms seen with primary infection.[7] Most commonly, episodes present as localized lesions that resolve within 6-10 days. Recurrent lesions can be painful or pruitic. Prior to a recurrence most patients experience prodromal symptoms such as itching or tingling at the site where the lesions appear.

Genital Herpes: Place in Therapy

Antiviral therapy provides clinical benefits to most patients with symptomatic genital herpes and is the mainstay of management.[12] Treatment with oral antivirals helps control signs and symptoms of genital herpes outbreaks. Treatment for primary infections of genital herpes includes early initiation of a 7-10-day course of antivirals. There are two ways to approach treatment of recurrent genital herpes infections. One approach is to treat each episode as it occurs with episodic therapy. The goal is to shorten the duration of the outbreak, reduce the pain and promote more rapid healing of lesions. Another approach is to initiate suppressive therapy with antivirals. With this method, antiviral medication is administered continuously to help suppress outbreaks before they occur rather than treat the outbreaks when they occur. The goal of therapy in this situation is to help prevent recurrences from happening, and to minimize viral shedding.[12] By reducing both recurrences and viral shedding, suppressive therapy helps reduce the risk of transmission of genital herpes. Suppressive therapy with Valtrex, when used in combination with safer sex practices, is the only antiviral proven to offer this benefit.

Several oral antivirals have been approved for use in the management of genital herpes including valacyclovir (Valtrex), acyclovir, and famciclovir (Famvir). However, Valtrex is the only anti-viral that offers once-daily dosing for the suppression of recurrent genital herpes in immunocompetent patients. Additionally, Valtrex is the only antiviral proven to reduce the risk of transmission of genital herpes when used as suppressive therapy in combination with safer sex practices. And Valtrex is the only antiviral proven to treat episodic outbreaks with a 3-day regimen.

GENITAL HERPES IN THE HIV-INFECTED PATIENT

Between 68-77% of HIV-infected, homosexual men possess antibodies to HSV 2 and almost as many are also seropositive for HSV 1. [28] [29] [30] As with most infections in immunocompromised patients, the frequency and severity of HSV disease is worsened in HIV-infected patients with severe immunodeficiency. Patients in the early stages of HIV infection and disease often present with chronic genital or anogenital herpes. As immune function decreases, the likelihood of infections (from reactivation of latent virus and acquisition of opportunistic organisms) increases. Latent HSV often reactivates in these patients and can cause severe recurrent HSV disease with tissue destruction and an extended course of viral shedding of HSV.

PLACE IN THERAPY

The principles guiding treatment of HIV-infected patients with genital herpes are the same as those for immunocompetent patients.

3.3 Disease Description of Herpes Zoster

Epidemiology

In the United States, there are approximately 500,000 cases of shingles per year. [31] [32] More than 90% of adults in the US are infected with the varicella-zoster virus and are at risk for herpes zoster. [33] The incidence of herpes zoster is highly dependent on age with individuals ≥50 years of age having the highest risk of reactivating the varicella-zoster virus. [31] Other patients at higher risk include patients with neoplastic diseases, patients receiving immunosuppressive medications, organ-transplant recipients, and individuals infected with HIV. [34]. Complications of herpes zoster are uncommon in individuals <60 years of age, and postherpetic neuralgia is reported to occur in fewer than 10% of patients under 30 years of age. The development of postherpetic neuralgia progressively increases with age to an incidence exceeding 60% in patients over 60 years of age. [35] During the period between 1982-1990, the Centers for Disease Control recorded 1064 deaths occurring due to herpes zoster. [36]

pathophysiology

Varicella-zoster virus is a herpesvirus that is responsible for two clinical syndromes: varicella (also known as chickenpox) which represents the primary infection and herpes zoster which represents the reactivated form. Once infected with the varicella-zoster virus, the virus becomes latent in the spinal ganglia. Herpes zoster is a vesicular skin rash generally occurring in single dermatomal distribution in immunocompetent patients. In addition, both acute and chronic pain is associated with reactivation of the latent virus in the nerve ganglion due to both demyelination and active viral replication. The pain may last several months

to years.[37] In immunocompromised patients, dissemination may occur and spread of the virus to other dermatomes (usually adjacent) is likely.

Clinical presentation

The occurrence of acute herpes zoster is often heralded by the onset of radicular pain. For many people, this pain may be incapacitating. The pain associated with herpes zoster is often characterized as aching, itching, or burning, and may be accompanied by severe stabbing pains, dysesthesia, paresthesia or hyperesthesia. [35] During prodrome patients may also experience headache, photophobia and malaise, but seldom fever. [34] Skin lesions will usually appear after one to five days. Cutaneous manifestations begin as an erythematous maculopapular rash that progresses to small clusters of vesicles. These vesicles will form pustules and then crust over. The eruptions are most commonly unilateral and do not cross the midline. Typically only one dermatome in the thoracic region is affected although it is not uncommon for vesicles to form in an adjacent dermatome. Healing occurs over a two to four week period and frequently results in scarring or pigment changes.

One of the most difficult complications of herpes zoster is the development of postherpetic neuralgia which is defined as pain, which persists after rash healing, or pain, which is present 30 days after rash onset. [34] The incidence of PHN increases with increasing age and occurs in over 60% of patients older than 60 years of age.[38] Other complications of the disease include encephalitis, myelitis, cranial and peripheral nerve palsies, delayed contralateral hemiparesis and visceral involvement. [34]). Ophthalmic involvement, which can lead to visual impairment, can also occur. Although these complications can occur in immunocompetent patients, complications are most likely to occur in patients who are immuocompromised.[37]

treatment approaches

(Pharmacological and Non-Pharmacological Options) Various treatment modalities have been used for the treatment of herpes zoster infections. Antiviral therapy is the preferred and most accepted form of therapy. Early initiation of an antiviral agent is key to reducing viral replication quickly and thus having the most potential to prevent nerve damage by inhibiting actively replicating virus in the nerve root. Antiviral agents accelerate the healing of cutaneous lesions, reduce the severity of acute pain and can reduce the duration of post-herpetic neuralgia. Corticosteroids when used in combination with certain antivirals have shown to accelerate healing, alleviate acute pain, and improve quality of life measures. Other drug therapies have been evaluated in an attempt to decrease or minimize the pain associated with postherpetic neuralgia including tricyclic antidepressants, gabapentin, and opioids. The use of sterile, non-occlusive, nonadherent dressings and keeping the lesions clean can help with symptomatic relief and prevention of bacterial infection. [34]

place in therapy

Antiviral therapy is commonly used for the treatment of herpes zoster. Currently there are three antiviral agents approved by the FDA for the treatment of herpes zoster: valacyclovir (Valtrex), acyclovir, and famciclovir (Famvir).

Valtrex, a prodrug of acyclovir, was designed to improve the bioavailability of acyclovir. Pharmacokinetic studies have shown that Valtrex produces acyclovir serum concentrations three to five times higher than oral acyclovir therapy. The enhanced bioavailability with Valtrex offers simple dosing for herpes zoster as compared to acyclovir.

Valtrex provides a treatment option that has been proven effective and well tolerated in the treatment of herpes zoster.

outcomes of therapy

Goals of therapy with herpes zoster include accelerating the healing of cutaneous lesions, reduce the severity of acute pain, and reduce the incidence, severity, and duration of post-herpetic neuralgia. [34]

Valtrex has been evaluated in three randomized, double-blinded trials, which included comparisons to placebo, acyclovir, and famciclovir. In a large, well-controlled trial, Valtrex 1 g three times daily for 7 days was more effective than oral acyclovir 800 mg five times daily for 7 days in the treatment of zoster associated pain (ZAP) and postherpetic neuralgia (PHN) in patients ≥50 years of age. [39] A subset

analysis of this data was performed and is the basis for the data found in the current Valtrex package insert. Median duration of pain after rash healing was 40 days in the Valtrex recipients and 59 days in patients receiving acyclovir, P=0.06.

Results from the only head-to-head trial between Valtrex and famciclovir indicate no significant difference in any parameter tested including PHN, ZAP, duration of abnormal sensations, time to rash healing, or safety profile.(5) This randomized, double-blind study compared Valtrex 1 g three times daily for 7 days to famciclovir 500 mg three times daily for 7 days in 597 immunocompetent patients.

In a placebo-controlled trial evaluating the safety and efficacy of Valtrex for the treatment of herpes zoster in immunocompetent patients <50 years of age, Valtrex reduced the median time to cessation of new lesion formation from 3 days with placebo to 2 days with Valtrex.(5) Although no difference was found with respect to post-herpetic neuralgia, patients younger than 50 years old are less likely to experience post-herpetic neuralgia.

4. PRODUCT DESCRIPTION

4.1 Generic Name, Brand Name and Therapeutic Class

Valtrex (valacyclovir hydrochloride) - antiviral

4.2 Dosage Forms and Package Sizes

Valtrex Caplets (blue, film coated, capsule shaped tablets) containing valacyclovir hydrochloride equivalent to 500 mg valacyclovir and printed with "*VALTREX* 500 mg." – Bottle of 30 (NDC 0173-0933-08) and unit dose pack of 100 (NDC 0173-0933-56). *Valtrex* Caplets (blue, film coated, capsule shaped tablets) containing valacyclovir hydrochloride equivalent to 1 gram valacyclovir and printed with "*VALTREX* 1 gram." Bottle of 21 (NDC 0173-0565 02).

4.3 NDC for All Formulations

Valtrex 500 mg (bottle of 30): NDC 0173-0933-08

Valtrex 500 mg (unit dose pack of 100): NDC 0173-0933-56

Valtrex 1 g (bottle of 21): NDC 0173-0565-02

See Enclosed Prescribing Information for *Valtrex* Caplets

4.4 AWP and WAC Cost per Unit

WAC*: *Valtrex* 1 g (bottle of 21) $146.74

WAC*: *Valtrex* 500 mg (bottle of 30) $115.10

Wholesale Acquisition Cost is the listed price to wholesalers and warehousing chains, not including prompt pays, stocking or distribution allowances, or other discounts, rebates or charge backs. *As of October 25, 2004

4.5 AHFS or Other Drug Classification

AHFS Drug Classification for *Valtrex* is: Antiviral, 8:18.

4.6 FDA Approved and Other Studied Indications

Refer to Enclosed Prescribing Information.

4.7 Use in Special Populations

Refer to Enclosed Prescribing Information.

4.8 Pharmacology

Table 1. Pharmacology of Acyclovir, Valacyclovir and Famciclovir[1,40,41]

Parameter	Acyclovir	Valacyclovir	Famciclovir
Formation of triphosphate	Acyclovir is phosphorylated to ACV-MP by viral thymidine kinase. Cellular enzymes convert the monophosphate to the diphosphate and then to the active triphosphate form (ACV TP).	See Acyclovir	After conversion to penciclovir, phosphorylation occurs in an identical manner to acyclovir
Mechanism of viral inhibition	Viral DNA polymerase incorporates ACV-TP into the viral DNA chain in place of the usual substrate, deoxyguanosine-TP. Viral DNA replication is immediately and completely terminated	See Acyclovir	PEN-TP is incorporated into viral DNA chain, but potentially allows viral DNA replication to continue.
Affinity for DNA polymerase	Affinity of ACV-TP > than affinity of PEN-TP	See Acyclovir	affinity of PEN-TP is lower than affinity for ACV-TP
Intracellular triphosphate concentrations in cells	Intracellular concentration of ACV-TP < PEN-TP concentration	See Acyclovir	Intracellular concentration of PEN-TP > ACV-TP concentration

KEY:

ACV-MP=acyclovir monophosphate; ACV-TP=acyclovir triphosphate, HepG2 cells=derived from human liver cells; MRC 5 cells=derived from human lung fibroblasts; PEN-TP=penciclovir triphosphate, VZV=varicella-zoster virus.

4.9 Pharmacokinetics/Pharmacodynamics

Key Clinical Pharmacokinetic Properties

Table 2. Key Clinical Pharmacokinetic Properties of Acyclovir, Valacyclovir and Famciclovir[1,40,41]

Pharmacokinetic Parameter	Acyclovir (oral)	Valacyclovir	Famciclovir
Oral bioavailability	10-20%*	54.5%	77%
Time to peak concentration	1.6 - 2.2[42]	1.5 – 1.8 hours	0.9 hours

*Bioavailability decreases with increasing dose.

KEY: AUC=area under the plasma concentration-time curve; Cmax=maximum plasma concentration; *=decrease(d), *=increase(d), Tmax=time to maximum plasma concentration.

Pharmacokinetic Parameter	Acyclovir (oral)	Valacyclovir	Famciclovir
Effect of food	No difference in peak or trough concentrations in fed vs. fasted state [43] Cmax and AUC significantly greater with light vs. heavy meal (no clinical importance) [44] May be taken without regard to meals	No clinically significant effect on acyclovir bioavailability after administration of VLT within 30 min of high-fat breakfast (51 g fat) May be taken without regard to meals	Penciclovir Cmax decreased approx. 50% and Tmax delayed 1.5 h when administered with food. No effect on AUC of penciclovir May be taken without regard to meals
Plasma protein binding	9-33%	13.5% - 17.9%	<20%
Plasma half-life **Normal renal function** **Renal Dysfunction**	2.5 – 3.3 hours 19.5 h (IV, Anuric)[45]	2.5 – 3.3 hours 14 h (ESRD)	2 –3 hours 13.4 hours (CrCl <20 ml/min)
Routes of excretion	Kidneys: 62 - 91%	See acyclovir	Kidneys: 73% Feces: 27%
Metabolism	Acyclovir is converted to a small extent to inactive metabolites by aldehyde oxidase and by alcohol and alcohol dehydrogenase Cytochrome P450 does not play a role in metabolism	Valacyclovir is converted to acyclovir (the active metabolite) and L-valine by first pass intestinal and/or hepatic metabolism. Acyclovir is converted to a small extent to inactive metabolites by aldehyde oxidase and by alcohol and aldehyde dehydrogenase. Cytochrome P450 does not play a role in metabolism.	Famciclovir is deacetylated and oxidized to form penciclovir, the active metabolite. Cytochrome P450 does not play an important role in metabolism.
Hemodialysis	• During hemodialysis: t1/2 ~ 5 h • Plasma acyclovir concentrations decreased approximately 60% during the six hour dialysis period • Dosage reduction and interval extension required as directed by package insert • A supplemental dose of acyclovir should be administered at the end of the hemodialysis period	• During hemodialysis: t1/2 ~ 4 h • One-third of acyclovir removed during a 4 hr dialysis session • Dosage reduction and interval extension required as directed by package insert • Should receive recommended dosage after hemodialysis	• Dosage reduction and interval extension required as directed by package insert • Dose after hemodialysis
Peritoneal Dialysis	No supplemental dose appears to be necessary after adjustment of the dosing interval	See acyclovir	No data available

*Bioavailability decreases with increasing dose.

KEY: AUC=area under the plasma concentration-time curve; Cmax=maximum plasma concentration; *=decrease(d), *=increase(d), Tmax=time to maximum plasma concentration.

4.10 Contraindications

Refer to Enclosed Prescribing Information.

4.11 Warnings/Precautions

Refer to Enclosed Prescribing Information.

4.12 Adverse Events

Table 3. Incidence (%) of Adverse Events in Herpes Zoster Study Populations[1]

Adverse Event	*Valtrex* 1 gm t.i.d. (n = 967)	Placebo (n = 195)
Nausea	15%	8%
Headache	14%	12%
Vomiting	6%	3%
Dizziness	3%	2%
Abdominal pain	3%	2%

Table 4. Incidence (%) of Adverse Events in Genital Herpes Study Populations[1]

	Genital Herpes Treatment			Genital Herpes Suppression		
Adverse Event	*Valtrex* 1 gm b.i.d. (n = 1194)	*Valtrex* 500 mg b.i.d. (n = 1159)	Placebo (n = 439)	*Valtrex* 1 gm q. d. (n = 269)	*Valtrex* 500 mg q.d. (n = 266)	Placebo (n = 134)
Nausea	6%	5%	8%	11%	11%	8%
Headache	16%	15%	14%	35%	38%	34%
Vomiting	1%	<1%	<1%	3%	3%	2%
Dizziness	3%	2%	2%	4%	2%	1%
Abdominal pain	2%	1%	3%	11%	9%	6%
Dysmenorrhea	<1%	<1%	1%	8%	5%	4%
Arthralgia	<1%	<1%	<1%	6%	5%	4%
Depression	1%	0%	<1%	7%	5%	5%

Table 5. Incidence (%) of Laboratory Abnormalities in Herpes Zoster and Genital Herpes Study Populations[1]

	Herpes Zoster		Genital Herpes Treatment			Genital Herpes Suppression		
Laboratory Abnormality	*Valtrex* 1 gm b.i.d.	Placebo	*Valtrex* 1 gm b.i.d.	*Valtrex* 500 mg b.i.d.	Placebo	*Valtrex* 1 gm q.d.	*Valtrex* 500 mg q.d.	Placebo
Hemoglobin (<0.8 x LLN)	0.8%	0%	0.3%	0.2%	0%	0%	0.8%	0.8%
White blood cells (0.75 x LLN)	1.3%	0.6%	0.7%	0.6%	0.2%	0.7%	0.8%	1.5%
Platelet count (<100,000/mm^3)	1.0%	1.2%	0.3%	0.1%	0.7%	0.4%	1.1%	1.5%
AST (SGOT) (>2 x ULN)	1.0%	0%	1.0%	*	0.5%	4.1%	3.8%	3.0%

Serum creatinine (>1.5 x ULN)	0.2%	0%	0.7%	0%	0%	0%	0%	0%
*Data were not collected prospectively LLN= lower limit of normal ULN= upper limit of normal								

Refer to Enclosed Prescribing Information.

4.13 Other Clinical Considerations

Refer to Enclosed Prescribing Information.

4.14 Drug/Food/Disease Interactions

Refer to Enclosed Prescribing Information.

4.15 Dosing and Administration

Refer to Enclosed Prescribing Information.

4.16 Co-prescribed/Concomitant Therapies

Refer to Enclosed Prescribing Information.

4.17 Product Comparisons

Comparisons

Table 6. Comparison of FDA Approved Indications and Dosage Regimens [1,40,41]

	Valtrex	**Acyclovir (Oral)**	**Famciclovir**
Treatment of Initial Episode of Genital Herpes§	Approved Indication 1 gm BID x 10 days	Approved Indication 200 mg 5x daily x 10 days	Not An Approved Indication
Treatment of Episodic Recurrences of Genital Herpes§	Approved Indication 500 mg BID x 3 days	Approved Indication 200 mg 5x daily x 5 days	Approved Indication 125 mg BID x 5 days
Suppressive Therapy for Recurrent Genital Herpes in Immunocompetent Adults	Approved Indication 1 g daily or 500 mg daily*	Approved Indication 400 mg BID (alternatives regimens include 200 mg 3x daily to 200 mg 5x daily)	Approved Indication 250 mg BID
Suppressive Therapy for Recurrent Genital Herpes in HIV-infected Patients†	Approved Indication 500 mg BID	Not An Approved Indication	Not An Approved Indication
Treatment of Recurrent Mucocutaneous Herpes Simplex Infections in HIV-infected Patients	Not An Approved Indication	Not An Approved Indication	Approved Indication 500 mg BID x 7 days
Reducing the Risk of Transmission of Genital Herpes‡,§	Approved Indication 500 mg daily	Not An Approved Indication	Not An Approved Indication
Treatment of Herpes Zoster§	Approved Indication 1 g TID x 7 days	Approved Indication 800 mg 5x daily x 7-10 days	Approved Indication
Treatment of Cold Sores (Herpes Labialis)§	Approved Indication 2 g BID x 1 day	Not An Approved Indication	Not An Approved Indication

Treatment of Chickenpox§	Not An Approved Indication	Approved Indication Children: 20 mg/kg 4 times daily (80 mg/kg/day) x 5 days Adults and Children >40 kg: 800 mg 4 x daily for 5 days	Not An Approved Indication
KEY: *An alternative dose for patients with < 9 recurrences per year †In HIV-infected patients with CD4 cell count ≥100 cells/mm^3 ‡ When used as suppressive therapy in combination with safer sex practices §In otherwise healthy adults			

5. PIVOTAL EFFICACY AND SAFETY TRIALS

5.1 Herpes Labialis

HSV-1 (herpes simplex virus type-1) is typically associated with herpes labialis (cold sores). Initial infection is usually asymptomatic, but can be variable. Following initial infection, the virus establishes latency and subsequently recurs at varying intervals throughout the person's lifetime. (7) Upon reactivation, the virus travels to the peripheral epithelium and replicates to manifest as a cold sore. Within 2-3 cycles of viral replication, a clinically apparent cold sore lesion can form. Most individuals who experience recurrences have 3 or 4 per year.(8)

Recurrent herpes labialis is often preceded by prodromal symptoms that include pain, tingling or itching. These symptoms may last up to 6 hours, and occasionally up to 24 to 48 hours.(9) Lesion outbreaks occur in 90% of patients who have experienced the prodromal stage.(10) Painful, fluid-filled vesicles (cold sores, fever blisters) commonly appear on the vermilion border of the lip within 12 hours of the first indication of skin induration or papule. These vesicles rupture rapidly and form nondescriptive ulcers. The time course for lesions to progress from the vesicle to the ulcer/crust stage is approximately 48 hours.(9) Viral shedding is most prominent early in the course of the disease (vesicular/ulcer stage). Vesicular-associated pain is most severe within the first 24 hours after the initial appearance of the lesions.(9) The healing process usually is complete within 8 to 10 days.

clinical information

Two large clinical trials were conducted with *Valtrex* for the episodic treatment of HSV-1 (herpes simplex virus type 1) infections. One of the trials was designed to assess the efficacy of 2 dosage regimens of *Valtrex* vs. placebo (taken at prodrome) on preventing the progression of cold sore lesion development. The other trial was designed to assess the same dosage regimens in reducing the duration of the cold sore episode. Information on study design, patient population, combined results and comments about the clinical trials with *Valtrex* are included in Table 7. The dosing regimens chosen for this protocol were designed to optimize the antiviral effects needed to counteract the rapid development of cold sore lesions. By achieving and maintaining high plasma levels of acyclovir, which are above the HSV-1 ED99 level during the period of early viral replication, it may be possible to interrupt the 2 to 3 cycles of viral replication that are thought to be necessary to produce clinically apparent lesions.(7)Specific results of these studies are presented below.

Table 7. *Valtrex* vs. Placebo for the Treatment of Herpes Labialis Lesions [11,46]

Study Design/Patient Information	Treatment Regimens	Results/Comments
• Two Multicenter (U.S.) studies • Randomized,double-blind, placebo-controlled study • Otherwise healthy patients ≥ 12 y w/ at least 3 episodes in previous year • Pt kept lesion diaries • Study drug was pt-initiated at first prodrome prior to lesion development • Investigators evaluated pt daily until lesion resolution	Study 1 • ITT population = 902 • VLT 2 g PO BID x 1 d followed by 1 g PO BID x 1 d (n=299) vs. • VLT 2 g PO BID x 1 d (n=311) vs • Matching PBO (n=292) Study 2 • ITT population = 954 • VLT 2 g PO BID x 1 d followed by 1 g PO BID x 1 d (n=339) vs. • VLT 2 g PO BID x 1 d (n=298) vs. • Matching PBO (n=317)	**Study Endpoints** • Duration of episode of herpes labialis: primary endpoint in Study 1 & secondary endpoint in Study 2 • Proportion of pt in whom development of cold sore lesion is blocked/prevented (aborted episodes = no progression to vesicle): primary endpoint in Study 2 and secondary endpoint in Study 1 • Other endpoints of both studies: time to lesion healing, time to cessation of pain/discomfort **Combined Results** • Complete resolution of episodes – 16% faster in patients receiving *Valtrex* vs. placebo (approximately one day faster, $P<0.001$) based on clinician assessment. • Lesion healing – 20% faster in patients taking *Valtrex* vs placebo (4.9 vs. 6.3 days, respectively, $P<0.001$). • Cessation of pain/discomfort – 25% faster in patients taking *Valtrex* vs. placebo (2.2 vs. 2.9 days, respectively, $P<0.001$). **Safety Profile** • Incidence of adverse events was similar across all treatment groups and included headache (14% vs. 10%), nausea (5% vs. 6%), diarrhea (4% each) and dizziness (2% vs. 1%). • No serious adverse events were reported.

KEY: BID=twice daily; d=day(s) or daily; d/c=discontinued; g=gram(s), hx=history; h=hour(s); ITT= Intent to treat; mo=month, PBO=placebo; PO=oral; pt=patient(s); tx=treatment or treated; VLT=*Valtrex* y=year(s), w/=with, w/n=within

Table 8. Duration of Cold Sore Episode

	Placebo	*Valtrex* 1 day	*Valtrex* 2 day
Study 1	N=292	N=311	N=299
Number of days (median)	5	4	4.5
Difference = VLT minus PBO		-1.0*	-0.5†
Number of days (mean)	6.1	5	5.3
Difference = VLT minus PBO		-1.1	-0.7
Study 2	N=317	N=298	N=339
Number of days (median)	5.5	5	5
Difference= VLT minus PBO		-0.5‡	-0.5‡
Number of days (mean)	6.3	5.3	5.5
Difference= VLT minus PBO		-1	-0.8

*=P value of 0.001.
†=P value of 0.009.
‡=P value of< 0.001,
PBO=placebo, VLT=*Valtrex*

Table 9. Prevented/Blocked Cold Sore Lesions

	Placebo	Valtrex 1 day	Valtrex 2 day
Study 1	**N=292**	**N=311**	**N=299**
Patients with prevented/blocked lesions (%)	111 (38)	138 (44)	139 (46)
OR* (95%CI)		1.32 (0.95 to 1.84)Ŧ	1.38 (0.98 to 1.94) ŧ
Study 2	**N=317**	**N=298**	**N=339**
Patients with prevented/blocked lesions (%)	112 (35)	129 (43)	147 (43)
OR* (95% CI)		1.39 (0.99 to 1.95)§	1.41 (1.02 to 1.94)**

*Odds ratios compare *Valtrex* to placebo.
†=P value of 0.096.
‡=P value of 0.061.
§ =P value of 0.0541
.**=P value of 0.036.

Table 10. Time to Cold Core Lesion Healing

	Placebo	*Valtrex* 1 day	*Valtrex* 2 day
Study 1	N=292	N=311	N=299
Patients progressing to crust (n) (%)	171 (59)	164 (53)	142 (47)
Number of days (median)	5.1	4.3	4.3
Difference = VLT minus PBO		-0.8*	- 0.8 †
Number of days (mean)	6.1	4.8	5
Difference = VLT minus PBO		-1.3	-1.1
Study 2	N=317	N=298	N=339
Patients progressing to crust (n) (%)	192 (61)	161 (54)	170 (50)
Number of days (median)	5.4	4.8	4.6
Difference		-0.6*	-0.8 *
Number of days (mean)	6.4	5.1	5.2
Difference = VLT minus PBO		-1.2	-1.2

*= P value of < 0.001.
†=P value of 0.001.,
PBO=placebo, VLT=*Valtrex*

Table 11. Time to Cessation of Pain and/or Discomfort

	Placebo	*Valtrex* 1 day	*Valtrex* 2 day
Study 1	N=292	N=311	N=299
Number of days (median)	1.8	1.2	1.3
Difference= VLT minus PBO		-0.6*	-0.5†
Number of days (mean)	2.9	2.1	2.5
Difference= VLT minus PBO		-0.7	-0.4
Study 2	N=317	N=298	N=339
Number of days (median)	2.2	1.5	1.5
Difference= VLT minus PBO		-0.7‡	-0.7§
Number of days (mean)	3.1	2.3	2.8
Difference = VLT minus PBO		-0.8	-0.3

*=P value of 0.009.
†=P value of 0.008.
‡ =P value of< 0.001.
§=P value of 0.003,
PBO=placebo, VLT=*Valtrex*

Table 12. Most Common Adverse Events

AE	Placebo		*Valtrex* 1 Day		*Valtrex* 2 Day	
	Study 1	Study 2	Study 1	Study 2	Study	Study 2
Headache	12 (4)	16 (5)	27 (9)	29 (10)	28 (9)	29 (9)
Nausea	12 (4)	17 (5)	12 (4)	13 (4)	16 (5)	13 (4)
Diarrhea	9 (3)	10 (3)	11 (4)	6 (2)	8 (3)	5 (1)

Dizziness was also reported by 2% of individuals receiving *Valtrex* and 1% of placebo-treated patients.

The approved dosage regimen of *Valtrex* for the treatment of cold sores is 2 g twice daily for 1 day with doses taken about 12 hours apart. Treatment should not exceed 1 day (2 doses of 2 grams in 24 hours). Therapy beyond 1 day does not provide additional clinical benefit.(1)

Given the dosage recommendations for treatment of cold sores, special attention should be paid when prescribing *Valtrex* for cold sores in patients who are elderly or who have impaired renal function. Dosage adjustments should be made in patients with varying degrees of renal dysfunction.(1)

5.2 Management of Genital Herpes

use in the treatment of intial (first episode) infections

In a controlled clinical trial in immunocompetent adults, 10-day courses of orally administered Valtrex 1 g PO BID (twice daily) and orally administered acyclovir 200 mg PO five times daily were equally effective in reducing the duration of viral shedding, reducing the time to pain cessation, and promoting the complete healing of lesions in patients with first episode genital herpes infections. (47) Adverse events were similar between patients receiving Valtrex and those receiving acyclovir. Adverse events reported in 2% of patients in this clinical trial included headache, nausea, rhinitis, pharyngitis and secondary infections. The most common event was headache in which the frequency was 13% for those treated with Valtrex 1 g and 10% for those treated with acyclovir 200 mg. Information on study design, drug regimens and results of the trial comparing Valtrex with acyclovir in first episode genital herpes infections is summarized in Table.

Table 13. Oral Valtrex vs. acyclovir for the Treatment of Initial Genital Herpes Infections [47]

Study Design Patient Population	Drug Regimen	Results/Comments
• International; Multicenter; Randomized; Double-blind; Active Control • Immunocompetent pt w/ first episode genital herpes • Age >18 y • Serologies were performed to differentiate pt with true primary vs. non-primary, first-episode genital herpes. • The proportion of each type of genital herpes was similar between the groups: True primary= 16%- 18% Non-primary= 81%- 83%	• VLT 1 g PO BID x 10 d (323 pt) • ACV 200 mg PO 5x/d x 10 d (320 pt) • Tx was initiated within 72 h of lesion onset.	**Primary efficacy parameters:** VLT ACV P Median time to healing of all lesions 9.0 d 9.0 d NS Median duration of viral shedding 3.0 d 3.0 d NS • VLT and ACV were equally effective in promoting complete healing of lesions. • Additional analyses suggested that patients with true primary infection healed more slowly than patients with non-primary infection (P=0.08). Although not statistically significant, pt initiating therapy w/n 2 days of lesion onset healed faster than those who began treatment later (P=0.15). • No difference in the duration of viral shedding between the two groups, however, additional analyses suggested that the duration of viral shedding was longer in pt with true primary vs. non-primary infection (p=0.08). **Secondary efficacy parameters:** VLT ACV P Proportion of pt forming New lesions after 48h 22% 24% NS Maximum (mean) number of lesions 10.5 12.1 NS Median duration of pain 5.0 d 5.0 d NS Time to loss of pain + clinical symptoms 9.0 d 9.0 d NS * Length of episode 13.0 d 13.0 d NS Time to crust formation (males only) 2.0 d 2.0 d NS Additional analyses suggested that the cessation of pain, urogenital and systemic signs and symptoms of genital herpes was achieved more rapidly in males than in females. Note: Length of episode includes all the times to event for lesion healing, loss of pain and loss of all other clinical signs and symptoms. **Adverse events:** • Nature and magnitude of adverse events were similar between groups. • Adverse events reported in >2 % of pt in this clinical trial included headache, nausea, rhinitis, pharyngitis and secondary infections. • The most common event in this study was headache in which the frequency was: VLT 1 g (13%), ACV 200 mg (10%)
ACV=Acyclovir, BID=Twice daily, d=Day(s), d/c=Discontinued, g=Gram(s), h=Hour(s), mg=Milligrams, NS=Not significant, PO=Oral, pt=Patient(s), RGH=Recurrent genital herpes, VLT=Valtrex, tx=Treatment/therapy, w/=With, w/n=Within, y=Year(s)		

use in episodic treatment of recurrent genital herpes

Valtrex 3-day Regimen

Previous studies have shown that Valtrex 1 g PO BID for 5 days is clinically equivalent to acyclovir 200 mg PO five times daily and significantly better than placebo for the episodic treatment of recurrent genital herpes in immunocompetent patients.[48,49] Although first approved for five-day therapy, the dosing regimen for the episodic treatment of genital herpes is now 500 mg BID for three days.[2] Valtrex received the short course indication June 25, 2001. A randomized, double-blind, multicenter trial was conducted among 1,170 immunocompetent patients to evaluate the efficacy of a 3-day vs. a 5-day course of therapy with Valtrex for the episodic treatment of genital herpes. The results of this study show that three and

five-day course of therapy with Valtrex 500 mg BID for the episodic treatment of genital herpes infections are equivalent in terms of median time to lesion healing, median duration of pain, median length of episode and proportion of patients with aborted (non-progressing) lesions. The most common adverse events that were reported during the Valtrex 3 vs. 5 day trial for episodic treatment of genital herpes included headache (10% vs.10%) nausea (4% vs. 4%) diarrhea (2% vs. 4%) and fatigue (2% vs.1%), respectively. .Details in regards to study design, dosing regimens and results are presented in Table 14.

Table 14. Three-Day vs. Five-Day Therapy with Valtrex for the Treatment of Genital Herpes

Study Design/ Patient Information	Dosing Regimens	Results/Comments
•Randomized, double-blind, multicenter •Otherwise healthy adults w/ hx of 4 recurrences in previous y or 2 episodes in previous 6 mo •N=1170 (800 pt randomized) •≥18 y • F-63%; M-37% • Pt evaluated for 6 d then twice weekly until lesions healed	• VLT 500 mg PO BID x 5d (n=398) • VLT 500 mg PO BID x 3 d, then PBO x 2 d (n=402) • Tx initiated w/n 24h of Sx of genital herpes	**Efficacy:** VLT-3d VLT-5d • Median time to lesion healing 4.4 d 4.7 d • Median duration of pain 2.9 d 2.5 d • Median length of episode 4.3 d 4.4 d • Halted progression of lesions 25.4% 26.6% • No significant difference was detected between 3 and 5 days of Valtrex in median time to lesion healing. • In men, the median duration of pain was 2.0 d in the VLT 5-d group and 2.4 d in the VLT 3-d group • In women, the median duration of pain was 2.9 d in the VLT 5-d group and 3.0 d in the VLT 3-d group • No difference in length of episode between the tx groups **Safety:** • Adverse events reported for 3 vs. 5 day therapy with Valtrex included: headache (10% for each), nausea (4% for each), diarrhea (2% vs. 4%) respectively), and fatigue (2% vs. 1%, respectively).
AE's=Adverse events, BID=Twice daily, d=Day(s), F=Female, hx=History, M=Male, PBO=Placebo, pt=Patient(s), Sx=Symptoms, pt=Patient(s), tx=Treatment, w=With, w/n=Within, y=Year(s)		

5.3 Reduction of Transmission of Genital Herpes

Background

The majority of people infected with herpes simplex virus (HSV) are unaware that they have genital herpes either because they have symptoms but do not recognize them, or they have asymptomatic infection. (50) Genital herpes symptoms do not have to be present to infect another individual. In fact, one study showed that up to 70% of genital herpes may be spread by people who are asymptomatically shedding virus. (15) Asymptomatic viral shedding can be identified from many anatomical sites and various body fluids in the absence of genital lesions in both men and women. Most patients with genital herpes experience asymptomatic shedding, which often occurs independent from an outbreak. (26) (27)

Clinical studies have shown that among couples discordant for HSV-2, the rate of transmission may be in the order of 3.5-10% per year. (15) (14,16) In these studies, patients were counseled on safer sex practices, including the use of condoms. Risk factors for transmission involve both biological and behavioral characteristics. Persons at a higher risk for acquiring genital herpes include females, those with frequent sexual activity, and those who are HIV seropositive.(15) (18,51)

Valtrex was compared to placebo for the reduction in the risk of transmission of HSV-2 genital herpes in healthy heterosexual monogamous couples discordant for the presence of HSV-2 antibody. (4) The HSV-2 seropositive source partner was randomized in a 1:1 ratio to receive *Valtrex* 500mg once daily or placebo for 8 months. The 8-month study period was considered sufficient to achieve the study objectives without being unnecessarily protracted. It was important to minimize the duration of the study, given the personal and intrusive nature of the study for both the source and susceptible partner. The

source partner had a history of 9 or fewer genital herpes episodes per year (making the *Valtrex* 500mg once daily dose an appropriate regimen). The HSV-2 seronegative susceptible partner was monitored for clinical and subclinical (serological) acquisition of HSV during the 8-month study period. Couples were offered condoms and counseled on safer sexual behavior throughout the study. In this controlled clinical trial, the anticipated transmission rate for placebo was 3% over an 8-month period. This is the first randomized controlled study of an antiviral demonstrating a reduction in sexual transmission of an infection. Further information about this study including patient population, study design, drug regimen, and results are shown in Table 15.

Table 15. - See Appendix

As previously discussed, all patients were counseled on safer sex practices including the use of condoms. A secondary analysis was done where symptomatic and overall acquisition were assessed within each of the three stratifications of condom use, which included 'never', 'sometimes', or 'nearly always'. [4] *Valtrex* provided benefit over placebo across all levels of condom use. Results of this analysis are shown in Figures 1 and 2. Despite regular counseling on safer sex practices, 37% of couples reported 'never' using condoms during vaginal or anal intercourse. *Valtrex* is indicated to reduce the risk of heterosexual transmission of genital herpes when used as suppressive therapy in combination with safer sex practices.

Figure 1. Symptomatic Acquisition by Condom Use

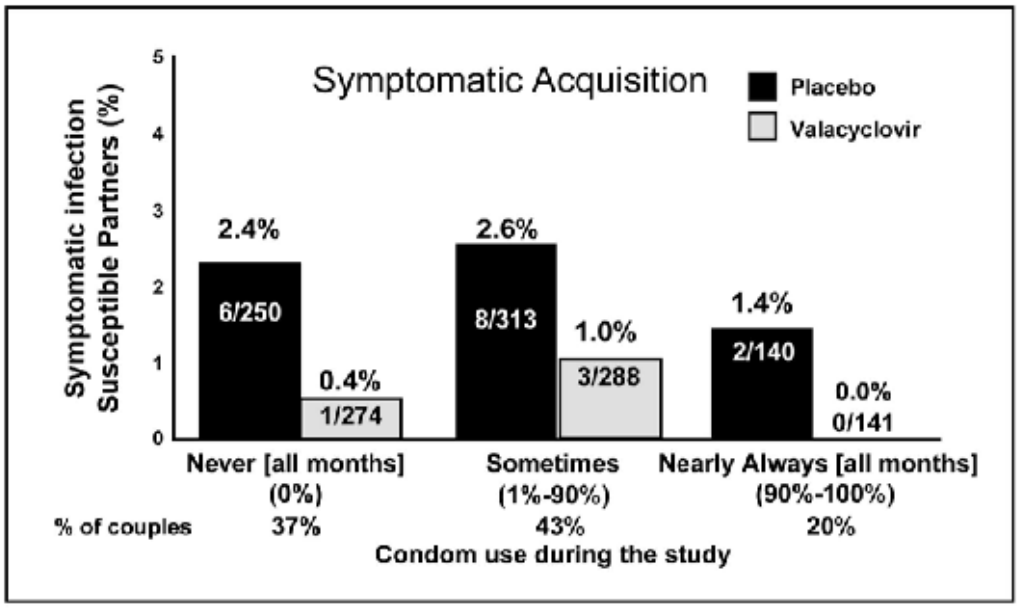
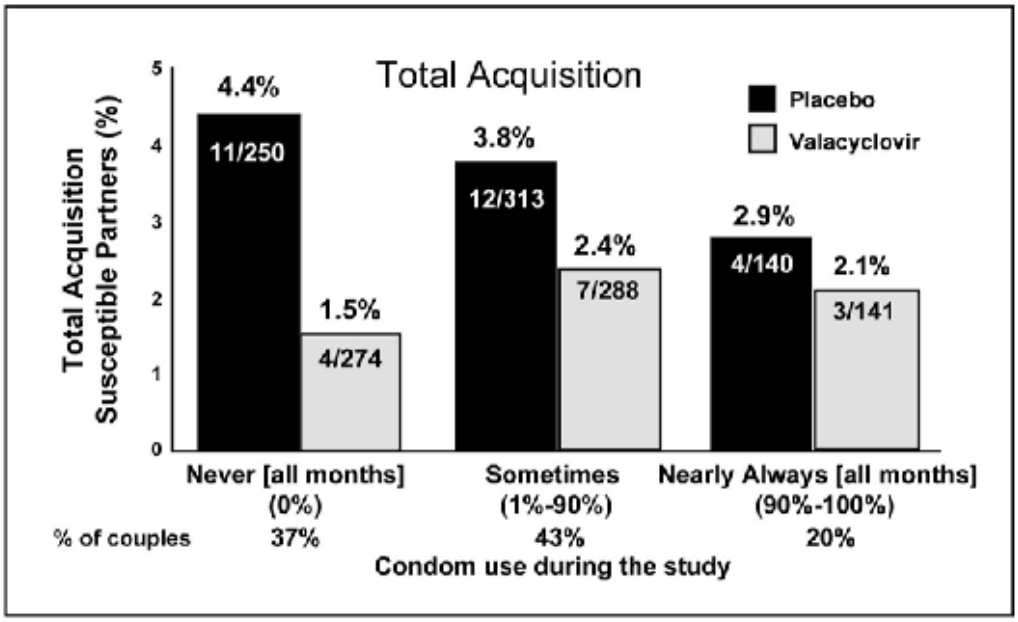


Figure 2. Overall Acquisition by Condom Use



Risk Factors Associated with Transmission

Covariate analysis was done to determine what factors contributed to the risk of transmission. In all patients, there was a significant increase in the risk of transmission associated with female susceptible partners, an increasing number of sexual contacts (<5 vs. 5-10 vs. >10), and when the source partners duration of infection was less than 2 years (vs. ≥2 years). (4)

Adverse Events

The adverse events reported by patients receiving *Valtrex* 500 mg once daily (n = 743) or placebo once daily (n = 741) included headache (*Valtrex* 29%, placebo 26%), nasopharyngitis (*Valtrex* 16%, placebo 15%), and upper respiratory tract infection (*Valtrex* 9%, placebo 10%). In this 8 month study, there were no clinically significant changes from baseline laboratory parameters in subjects receiving *Valtrex* compared with placebo. (1,4)

5.4 Suppression of Recurrent Genital Herpes in Patients with HIV

Valtrex was evaluated in a 6 month, multicenter, randomized, double-blind, placebo controlled study for the suppression of recurrent anogenital HSV infections in HIV-infected patients receiving antiretroviral therapy. (52) Patients were randomized to receive either *Valtrex* 500 mg twice daily (n=194) or placebo (n=99). The primary clinical outcome was the proportion of patients recurrence free of anogenital HSV at 6 months between treatment groups. Additionally the time to first recurrence of anogenital herpes, first culture-positive recurrence, and first oral HSV recurrence was evaluated. Patients were primarily male (88%) and had a median of 5 recurrences per year of genital herpes prior to intiating suppressive therapy. The median baseline plasma HIV RNA level was 2.6 $\log_{10}$ copies/ml in each treatment group and median baseline CD4 count was 313 cells/mm^3 for patients taking placebo and 336 cells/$mm^3$for those taking *Valtrex*.

The proportion of patients recurrence-free was significantly higher in those receiving *Valtrex* compared with placebo (65% vs. 26%, $P < 0.001$; RR=2.5; 95% CI, 1.8 - 3.5). The time to first anogenital HSV recurrence was significantly shorter for patients receiving placebo compared to those receiving *Valtrex* (median, 59 days vs. >180 days; HR=5.0; 95% CI, 3.30 - 7.7). A similar result was observed for the time to first culture-positive recurrence and first oral recurrence, both favoring *Valtrex* (HR=16.67; 95% CI, 1.40 - 2.36 and HR=5.26; 95% CI, 1.04 - 1.48, respectively). During the study, thirty-eight percent of

patients taking placebo reported a culture-positive recurrence compared to 15% taking *Valtrex*. Also, 15% of those receiving placebo reported a recurrence of oral herpes compared to 4% for those taking *Valtrex*.

The most frequently reported adverse events for *Valtrex* were headache, diarrhea, and upper respiratory tract infection. No reports of thrombotic thrombocytopenic purpura (TTP), hemolytic uremic syndrome (HUS), microangiopathy or patient death occurred during the study.

5.5 Herpes Zoster

BACKGROUND

In the United States, there are approximately 500,000 cases of shingles per year.[31,32] The incidence of herpes zoster is highly dependent on age with individuals ≥50 years of age having the highest risk of reactivating the varicella-zoster virus.[31] Complications of herpes zoster are uncommon in individuals ≤ 60 years of age, and post-herpetic neuralgia is reported to occur in fewer than 10% of patients under 30 years of age. The development of post-herpetic neuralgia progressively increases with age to an incidence exceeding 60% in patients over 60 years of age.[35]

Zoster-Associated Pain (ZAP) and Post-herpetic Neuralgia (PHN)

ZAP (zoster-associated pain) is a term which describes the evaluation of pain as a continuum rather than as arbitrarily determined time periods [i.e. - includes both acute and chronic pain, or post-herpetic neuralgia (PHN)]. PHN is defined as pain, which persists after rash healing, or pain, which is present 30 days after rash onset. Many medical experts accept the concept of ZAP as a clinically meaningful description of pain associated with herpes zoster.[53] However, for the purposes of antiherpetic product labeling, PHN is defined (per FDA) as pain after rash healing.

DOSAGE AND ADMINISTRATION

The recommended dosage of *Valtrex* for the treatment of herpes zoster is 1g orally three times daily for 7 days. In patients with reduced renal function, reduction in dosage is recommended. Therapy should be initiated at the earliest sign or symptom of herpes zoster and is most effective when started within 48 hours of the onset of zoster rash. CLINICAL INFORMATION

Valtrex® is approved for the treatment of herpes zoster in immunocompetent adults. [1] The recommended dosage of *Valtrex* for the treatment of herpes zoster is 1 gram orally 3 times daily for 7 days. Therapy should be initiated at the earliest sign or symptom of herpes zoster and is most effective when started within 48 hours of the onset of zoster rash. The safety and efficacy of *Valtrex* initiated more than 72 hours after the onset of the zoster rash has not been established.

clinical Information: Prospective Studies

Valtrex vs. Acyclovir

In a clinical trial of *Valtrex* vs. acyclovir for the treatment of herpes zoster, *Valtrex* 1 g TID (three times daily) for 7 days was demonstrated to be more effective than acyclovir 800 mg five times daily for 7 days in the treatment of zoster associated pain (ZAP) and postherpetic neuralgia (PHN) in patients 50 years of age. ZAP was defined as all pain, which included acute or short-term pain while lesions were present and the persistent, chronic type of pain, usually referred to as postherpetic neuralgia. Postherpetic neuralgia was defined as pain after rash healing. Complete cessation of pain was defined as the time at which assessments for pain yielded no pain for 28 consecutive days with no further appearance or re-emergence of pain. Pain was assessed daily by determining the presence of pain, burning, other types of discomfort, or abnormal sensations (paresthesias, dysesthesias, hyperesthesia, itching, tingling, loss of feeling and extreme sensitivity to touch) during the first 30 days of the trial and weekly for 20 additional weeks ( ).

Patients receiving *Valtrex* experienced a median duration of pain (ZAP) which was significantly shorter than that of patients receiving acyclovir (Table 1). Intent-to-treat analyses of both ZAP and PHN were used in this comparative study (n=1141) of *Valtrex* and acyclovir. The difference between treatment arms (7 days vs. 14 days) of *Valtrex* was not statistically significant for either analysis. [39]

The *Valtrex* package insert describes results from a subset analysis of the data from this trial using a definition of pain, or PHN, as pain after rash healing. Median duration of PHN was 40 days in the *Valtrex* recipients and 59 days in patients receiving acyclovir. In this analysis a significant number of patients were

excluded for a variety of reasons; for example, no evidence of pain at the time of rash healing. This subset analysis lacked the number of patients required to detect a potential difference in treatment arms and a nonsignificant "p" value (P=0.06) was calculated. (39)

Valtrex vx. famciclovir

Results from a head-to-head trial between *Valtrex* 1 g TID for 7 days and famciclovir 500 mg TID for 7 days indicate no significant difference in any parameter tested including PHN, ZAP, duration of abnormal sensations, time to rash healing, or safety profile between these two products. The two groups were similar in terms of demographics with the exception of more patients receiving *Valtrex* had reported the occurrence of prodromal pain and more patients reported a more severe prodromal pain compared with patients receiving famciclovir. (5)

Valtrex vs. Placebo

Valtrex was compared with placebo for the treatment of herpes zoster in otherwise healthy patients 18-50 years of age (median age = 36 years).(54) *Valtrex* reduced the median time to cessation of new lesion formation from 3 days with placebo to 2 days with *Valtrex*. There were no statistically significant differences in duration of pain between recipients of *Valtrex* vs. placebo. Although, patients <50 years of age are much less likely to experience ZAP or PHN.

Herpes Zoster Ophthalmicus

A large, randomized controlled clinical trial assessing the safety and efficacy of *Valtrex* and acyclovir in patients >50 years of age (n=1141) with localized herpes zoster was conducted. An analysis of the subset of patients with herpes zoster ophthalmicus (n=119) showed that efficacy results for the primary endpoints were similar to the study as a whole. In addition, more than 90% of the patients had resolution of ocular signs or symptoms within 5 weeks. (39)

SAFETY PROFILE of VALTREX in HERPES ZOSTER

During clinical trials of *Valtrex* for herpes zoster in otherwise healthy adults, there were no significant differences in the frequency of adverse experiences between recipients of either *Valtrex* or acyclovir. Only nausea and headache were reported by more than 10% of patients in either treatment group. The most common adverse experiences with *Valtrex* were nausea, vomiting, headache, diarrhea, and constipation.(1)

5.6 Chickenpox

The use of *Valtrex* for treatment of chickenpox in pediatric patients 2 to <18 years of age is based on single dose pharmacokinetic and multiple dose safety data from an open label trial with valacyclovir and supported by safety and extrapolated efficacy data from 3 randomized, double blind, placebo controlled trials evaluating oral acyclovir in pediatric patients.

The single dose pharmacokinetic and multiple dose safety study enrolled 27 pediatric patients 1 to <12 years of age with clinically suspected VZV infection. Each subject was dosed with valacyclovir oral suspension, 20 mg/kg 3 times daily for 5 days. Acyclovir systemic exposures in pediatric patients following valacyclovir oral suspension were compared with historical acyclovir systemic exposures in immunocompetent adults receiving the solid oral dosage form of valacyclovir or acyclovir for the treatment of herpes zoster. The mean projected daily acyclovir exposures in pediatric patients across all age groups (1 to <12 years of age) were lower (Cmax: ↓13%, AUC: ↓30%) than the mean daily historical exposures in adults receiving valacyclovir 1 gram 3 times daily, but were higher (daily AUC: ↑50%) than the mean daily historical exposures in adults receiving acyclovir 800 mg 5 times daily. The projected daily exposures in pediatric patients were greater (daily AUC approximately 100% greater) than the exposures seen in immunocompetent pediatric patients receiving acyclovir 20 mg/kg 4 times daily for the treatment of chickenpox.

Based on the pharmacokinetic and safety data from this study and the safety and extrapolated efficacy data from the acyclovir studies, oral valacyclovir 20 mg/kg 3 times a day for 5 days (not to exceed 1 gram 3 times daily) is recommended for the treatment of chickenpox in pediatric patients 2 to <18 years of age. Because the efficacy and safety of acyclovir for the treatment of chickenpox in children <2 years of age have not been established, efficacy data cannot be extrapolated to support valacyclovir treatment in

children <2 years of age with chickenpox. *Valtrex* is also not recommended for the treatment of herpes zoster in children because safety data up to 7 days' duration are not available

6. ADDITIONAL SAFETY DATA

6.1 Long-Term Safety of Valtrex

The recommended dosage of *Valtrex* for chronic suppressive therapy of recurrent genital herpes is 1 g once daily in immunocompetent patients. In patients with a history of 9 or fewer recurrences per year an alternative dose is 500 mg once daily.[1] The safety and efficacy of therapy with *Valtrex* beyond 1 year have not been established. The Centers for Disease Control and Prevention (CDC) recommends that during suppressive antiviral therapy, patients should be reassessed periodically (e.g., annually) to determine the continued need for therapy.[55]

clinical information

Following an 8-month, double-blind, placebo-controlled clinical trial evaluating *Valtrex* 500 mg once daily for the reduction in the risk of transmission of genital herpes, a 12 month open-label suppression phase was conducted to collect up to 20 month safety data for *Valtrex*.[56] Of the 1484 source partners who participated in the double-blind phase of the study, 1018 elected to continue in the 12-month open-label suppression phase of the study (519 formerly randomized to *Valtrex*, 499 formerly randomized to placebo). For those source partners who were randomized to *Valtrex* during the double-blind phase and entered the open-label suppression phase the median number of days on which those source partners received *Valtrex* was 611 (range = 239-784 days). Eighty-one percent of patients completed the open-label phase.

The results showed no notable differences in the nature and incidence of adverse events observed between the 8-month, double-blind phase and the open-label phase of the study.[56] Headache, nasopharyngitis, and upper respiratory tract infection were the most commonly reported adverse events. There was no evidence of an increase in the overall incidence or nature of adverse events in the *Valtrex* group over time as compared to placebo. There were no clinically significant changes in laboratory values within the *Valtrex* group over time or between the *Valtrex* and placebo groups. *Valtrex* 500 mg once daily was generally safe and well tolerated in this study. Further details are outlined in Table 16 and Table 17.

Table 16. Clinically Significant Laboratory Abnormalities Double-Blind/Open-Label Suppression Phases[56]

	Placebo* (n = 499)	***Valtrex** (n = 519)*
Alkaline Phosphatase (>1.5 x NRH)	0/499	0/519
ALT (>2 x NRH)	20/499 (4%)	16/519 (3%)
Creatinine (>1.5 x NRH)	0/499	0/519
Hemoglobin (<0.8 x NRL)	1/498 (<1%)	5/519 (<1%)
Platelet Count (<100,000/mm3)	1/497 (<1%)	2/519 (<1%)
White blood cells (<0.75 x NRL)	11/498 (2%)	8/519 (2%)

Table 17. Summary of Frequently Reported Adverse Events in Double-Blind, Open-Label, and Double-Blind/Open-Label Suppression Phases[56]

	Double-Blind Phase (≤ 8 months)		**Open-Label Suppression Phase (≤ 12 months)**	**Double-Blind/Open-Label Phases (≤ 20 months)**	
Adverse Events	*Valtrex* (n = 519)	Placebo (n = 499)	Overall* (n = 1018)	*Valtrex*‡ (n = 519)	Placebo† (n = 499)
Any Event n (%)	439 (85)	414 (83)	656 (64)	465 (90)	444 (89)
Headache	174 (34)	152 (30)	162 (16)	197 (38)	174 (35)
Nasopharyngitis	102 (20)	90 (18)	121 (12)	131 (25)	117 (23)
Upper respiratory tract infection NOS*	55 (11)	61 (12)	72 (7)	73 (14)	82 (16)

*All subjects in open-label suppression phase on *Valtrex* 500 mg once daily.

†Source partners who received placebo during the double-blind phase followed by open-label *Valtrex* suppressive therapy

‡Source partners who received *Valtrex* during the double-blind phase followed by open-label *Valtrex* suppressive therapy.

NOS = Not Otherwise Specified

7. COMPARATIVE DATA

7.1 Valtrex compared to acyclovir for herpes zoster

***Valtrex* vs. Acyclovir in herpes zoster**

In a large, well-controlled clinical trial for the treatment of herpes zoster, *Valtrex* 1g three times daily for 7 days proved to be more effective than oral acyclovir 800 mg five times daily for 7 days in reducing the median duration of pain. Evaluations of pain included assessments of both ZAP and PHN. ZAP was defined as all pain, which included acute or short-term pain while lesions were present and the persistent, chronic type of pain, usually referred to as post-herpetic neuralgia. Post-herpetic neuralgia was defined as pain after rash healing. Complete cessation of pain was defined as the time at which assessments for pain yielded no pain for 28 consecutive days with no further appearance or re-emergence of pain. Pain was assessed daily by determining the presence of pain, burning, other types of discomfort, or abnormal sensations (paresthesias, dysesthesias, hyperesthesia, itching, tingling, loss of feeling and extreme sensitivity to touch) during the first 30 days of the trial and weekly for 20 additional weeks. [39] Patients receiving *Valtrex* experienced a median duration of pain (ZAP) which was significantly shorter than that of patients receiving acyclovir (Table 18). Intent-to-treat analyses all patients who experienced pain of both ZAP and PHN were used in this comparative study of *Valtrex* and acyclovir. [39]

The *Valtrex* package insert describes results from a subset analysis of the data from this trial using a definition of PHN, as pain after rash healing.[1] In this analysis a significant number of patients were excluded for a variety of reasons; for example, no evidence of pain at the time of rash healing. This subset analysis (n = 879) lacked the number of patients required to detect a difference in treatment arms ($P = 0.06$).

Table 18. *Valtrex* vs. Acyclovir for Treatment of Herpes Zoster in Immunocompetent Patients [39]

Study Design Patient Information	Dosing Regimens	Results/Comments
• Randomized; Double-blind; ZVR-controlled; Multicenter; International • 1141 immunocompetent pt ≥ 50 y • F = 648 (57%) • M =4 93 (43%) • Mean age = 68 y (range: 50-99 y); (80% of pt >60 y) (20% of pt 50-60 y) • 10% pt (119 pt) had HZO • Tx initiated w/n 72 h (most w/n 48 h) • Pt monitored for 6 mo	• VLT 1 g PO TID x 7d (n = 384) • VLT 1 g PO TID x 14d (n = 381) • ACV 800 mg 5x/d x 7d (n = 376)	**Median duration of pain (ZAP)** • VLT-7 = 38 d • VLT-14 = 44 d • ACV = 51 d • VLT for either 7 or 14 d significantly accelerated resolution of pain compared to ACV (*P*= 0.001 and *P* = 0.03, respectively). • VLT reduced the proportion of patients with pain persisting for 6 mo from 26% to 19% compared to pt receiving ACV (*P* =0.02) • Pain resolved approximately 34% faster in patients treated with VLT vs. ACV. • Older age, more severe pain at entry and presence of prodromal pain were predictive of longer lasting pain. **% pt with pain after rash healing:** • VLT-7 = 79% • VLT-14 = 80% • ACV = 85% **Median duration of pain after rash healing:** • VLT-7 = 30 d • VLT-14 = 35 d • ACV = 39 d • Hazard ratio=1.32, *P* = 0.002 for VLT-7 vs. ACV • Hazard ratio=1.32, *P* = 0.03 for VLT-14 vs. ACV **Pt with pain after rash healing per FDA analysis (n = 868):** • VLT-7 = 40 d • VLT-14 = 43 d • ACV = 59 d • Hazard ratio=1.21, *P* = 0.061 for VLT-7 vs. ACV • Hazard ratio=1.15, *P* = 0.175 for VLT-14 vs. ACV **% of pt with pain persisting beyond 30 d:** • VLT-7 = 49% • VLT-14 = 51% • ACV = 57% • VLT significantly accelerated the resolution of pain that persisted beyond 30 d • Hazard ratio: 1.24, *P* = 0.01 for VLT-7 vs. ACV • Hazard ratio: 1.17, *P* = 0.09 for VLT-14 vs. ACV

Study Design Patient Information	Dosing Regimens	Results/Comments
		Median duration of abnormal sensations: • VLT-7 = 45 d • VLT-14 = 38 d • ACV = 57 d • The median duration of abnormal sensations was significantly shorter in pt receiving VLT vs. ACV. **Concomitant analgesic use:** • Use of non narcotic analgesics • VLT-7 = 76% • VLT-14 = 75% • ACV = 82% • Use of opioids • VLT-7 = 53% • VLT-14 = 49% • ACV = 53% **Effect on skin lesions:** • Cutaneous efficacy parameters such as the median time to cessation of new lesion formation was similar (3 d for each group) and time to > 50% crusting and healing was also similar (5 d for each group). **Adverse Events:** • Adverse events were similar in nature and magnitude between the groups. Only nausea and headache were reported by more than 10% of pt in any of the 3 groups.
KEY: ACV=acyclovir, d=day(s), F=female, g=gram(s), h=hour(s), HZO=herpes zoster ophthalmicus, M=male, mg=milligrams, mo= month(s), (n)=number of patients, PHN=post-herpetic neuralgia, PO=oral, pt=patient(s), TID=three times daily, Tx=treatment/ treated/therapy, VLT=*Valtrex*, w/=with, wk=week(s), w/n=within, y=year(s), ZAP=zoster-associated pain		

7.2 Valtrex compared to famciclovir for herpes zoster

Valtrex versus Famciclovir in the treatment of herpes zoster

In a randomized, double-blind, multicenter clinical trial, *Valtrex* 1g TID (three times daily) was compared to famciclovir 500 mg TID for 7 days for the treatment of herpes zoster in 597 immunocompetent patients >50 years of age.(5) The two groups were similar in terms of demographics with the exception of more patients receiving *Valtrex* had reported the occurrence of prodromal pain and more patients reported a more severe prodromal pain compared with patients receiving famciclovir. The diagnosis of herpes zoster was clinically confirmed. Diaries were used to record information regarding ZAP (zoster-associated pain), burning, and discomfort in the dermatome of the affected area. Results from this study showed no difference in any parameter tested for herpes zoster including PHN (post-herpetic neuralgia), ZAP, duration of abnormal sensations, time to rash healing, or safety profile.(5) Table 19 summarizes the findings of this study.

Table 19. *Valtrex* vs. Famciclovir for Treatment of Herpes Zoster in Immunocompetent Patients [5]

Study Design	Dosing Regimens	Results/Comments
• Randomized; Double-blind; Controlled; Multicenter; International • 597 immunocompetent pt >50 y of age • Pt with HZO were excluded • F=63% M =37% • Median age=68 y (range: 33-95 y) • 73% of pt >60 y) • (27% of pt 50-60 y) • Tx initiated w/n 72 h (82% w/n 48 h) • Pt monitored for 6 mo: days 3, 8, 14, and 28, then qmo until 6 mo • Pt diary (day 1-28) for pain according to a 6 point scale, then weekly week 4 up to 6 mo	• VLT 1 g PO TID x 7d (n = 297) • FAM 500 mg PO TID x 7d (n = 300)	**Note:** Statistically significantly more pt (78% vs 70%) receiving VLT reported prodromal pain in addition more pt in the VLT arm (34% vs 24%) reported a more severe prodromal pain. **Note:** None of the pain comparisons listed below were statistically significant different between treatment groups. Loss of zoster associated pain (ZAP): • VLT 42d FAM 49d (HR 1.02) Loss of PHN from rash healing: • Intent- to- treat; includes all patients with pain duration of zero for those with no pain on or after rash healing • VLT 36d FAM 37d (HR 1.01) Loss of PHN from day 30 • Intent- to- treat; includes all pt with pain duration of zero for those with no pain on or after d 30 • VLT 15d FAM 19d (HR 1.01) Loss of PHN from rash healing: • Excludes pt with no pain on or after rash healing • VLT 42d FAM 44d (HR 1.01) Loss of PHN from d 30: • Excludes pt with no pain on or after d 30 • VLT 55d FAM 61d (HR 1.06) Loss of clinically significant pain: • Defined as pain of moderate or higher intensity • Pt with pain of mild or lower intensity at presentation and through follow-up were assigned a pain duration of zero • VLT 35d, FAM 35d (HR 0.99)

ACV=acyclovir, d=day(s), F=female, FAM=famiciclovir, g=gram(s), h=hour(s), HZO=herpes zoster ophthalmicus, M=male, mg=milligrams, mo=month(s), (n)=number of patients, PHN=post-herpetic neuralgia, PO=oral, pt=patient(s), q=every, TID=three times daily, Tx=treatment/treated/therapy, VLT=*Valtrex*, w/=with, wk=week(s), w/n=within, y=year(s), ZAP=zoster-associated pain.

Study Design	Dosing Regimens	Results/Comments
		Loss of abnormal sensations: • VLT 42d FAM 35d (HR 1.00) Proportional analysis: • Pt with pain on or after rash healing – VLT 86% FAM 87% • Pt with pain at one mo – VLT 34% FAM 62% • Pt with pain at 3 mo – VLT 32% FAM 34% • Pt with pain at 6 mo – VLT 19% FAM 19%
		100% rash healing: • 7d: VLT 32% FAM 25% • 14d: VLT 89% FAM 82% • 28d: VLT 96% FAM 99% Adverse events were similar in nature and magnitude between the groups. Headache and nausea were reported most frequently.
ACV=acyclovir, d=day(s), F=female, FAM=famiciclovir, g=gram(s), h=hour(s), HZO=herpes zoster ophthalmicus, M=male, mg=milligrams, mo=month(s), (n)=number of patients, PHN=post-herpetic neuralgia, PO=oral, pt=patient(s), q=every, TID=three times daily, Tx=treatment/treated/therapy, VLT=*Valtrex*, w/=with, wk=week(s), w/n=within, y=year(s), ZAP=zoster-associated pain.		

7.3 Valtrex compared to acyclovir for suppression of genital herpes

Genital Herpes-Suppressive Therapy

Valtrex is approved for the suppression of recurrent genital herpes in immunocompetent adults at a dosing regimen of 1 g once daily, with an alternative dosing regimen of 500 mg once daily for those patients with a history of 9 or fewer recurrences per year. Acyclovir is approved for the suppression of recurrent genital herpes at a dosing regimen of 400 mg twice daily. Alternative acyclovir regimens have included doses ranging from 200 mg three times daily to 200 mg 5 times daily. Results of a large, randomized, double-blind clinical trial in patients with a history of 6 or more recurrences per year showed *Valtrex* 1 g once daily was comparable to acyclovir 400 twice daily for the suppression of genital herpes [(3)]At the end of the one-year study period, 34% of patients receiving *Valtrex* 1 g once daily or acyclovir 400 mg twice were recurrence-free compared to only 4% of patients receiving placebo. Adverse events between *Valtrex* and acyclovir were similar in nature and incidence.

One Year Dose-Ranging Suppression Trial

Several doses of *Valtrex* were compared for suppression of recurrent genital herpes in a large, multicenter, randomized, placebo-controlled clinical trial involving over 1,400 patients with a history of 6 or more recurrences of genital herpes in the previous 12 months [(3)]. *Valtrex* oral dosage regimens which were evaluated included: Valtrex 250 mg (n=269), 500 mg (n=266), and 1 g (n=269) once daily and 250 mg twice daily (n=274). These were compared to acyclovir 400 mg twice daily (n=267) and placebo (n=134). The study evaluated recurrence rates over a 1-year period. All clinically confirmed recurrences were treated with *Valtrex* 1 g twice daily for 5 days. Several types of analyses were performed, and data were stratified into groups based on the patients' frequency of recurrences (greater than or less than 9 recurrences per year).

The results of this trial showed that patients with more frequent recurrences per year responded best to a 1 g once daily dose of *Valtrex*. In patients with 9 or fewer recurrences per year, good results were obtained with Valtrex 500 mg once daily. Based on analysis of crude proportions, 34% of patients were recurrence-free at 12 months with once daily Valtrex 1 g as compared to 4% with placebo. In patients with

9 or fewer recurrences, 31% of patients were recurrence-free with *Valtrex* 500 mg daily as compared to 3% with placebo . Further results are presented in Table 20 below.

Adverse events were generally mild, infrequent and similar in nature to placebo. The most common adverse event reported in all groups was headache which was reported by 35%, 38%, and 34% of patients taking Valtrex 1 g, Valtrex 500 mg and placebo, respectively.

Table 20. Proportion of Patients Recurrence Free at 12 months

Regimen	Percent of pts rec free at 12 mo (<9 rec/y)		Percent of pts rec free at 12 mo (>10 rec/y)		Percent of pts rec free at 12 mo (All Patients)		Reduction in yearly rec rate (%)
	*	†	*	†	*	†	
VLT 1 g PO QD	36	50	32	47	34	48	78
VLT 500 mg PO QD	31	46	23	30	28	40	71
VLT 250 mg PO QD	16	27	13	16	15	22	54
VLT 250 mg PO BID	42	59	26	40	34	50	79
ACV 400 mg PO BID	35	53	34	45	35	49	79
PBO	3	3	6	8	5	5	

* Based on analysis of crude proportions; all doses of *Valtrex* were significantly ($p<0.0001$) more effective than PBO in preventing or delaying recurrences of genital herpes Note: Crude proportions analysis is the worst case scenario because many patients in the VLT arm of the trial withdrew before the end of the year and did not have a recurrence. However, for statistical purposes, these patients were considered "failures" even though they did not have a recurrence. Few of the pts in the PBO arm withdrew (they kept getting recurrences). So the analysis is biased in favor of the PBO arm of the trial.

† Based on Kaplan-Meier estimates of proportions based on the time-to-event analysis.

ACV=Acyclovir, BID=twice daily, g=gram(s), mo=month, PBO=placebo, PO=oral, pop=population, Pt=patient(s), QD=once daily, rec=recurrence, VLT=Valtrex, y=year(s)

7.4 Valtrex compared to famciclovir for suppression of genital herpes

Valtrex versus Famciclovir in Suppression of Recurrent genital herpes

Two, randomized, double-blind, double-dummy, studies compared famciclovir 250 mg BID (twice daily) and *Valtrex* 500 mg QD in patients with genital herpes [HSV(herpes simplex virus)-2 or HSV-1] based on the hypothesis that daily famciclovir would be superior to *Valtrex.*[57] Study 1 evaluated the suppression of clinical genital herpes recurrences for 16 weeks.

Study 1 was conducted between February and October 1997 among 320 adult patients with recurrent genital herpes. Patients had a history of ≥ 6 recurrences in the previous year. Diagnosis was based on clinical criteria and/or serology tests. summarizes additional study information, including study findings.

Table 21. *Valtrex* versus Famciclovir in Suppression of Recurrent Genital Herpes [57]

Study Design /Patient Information	Dosage Regimen	Results /Comments
• Randomized, double-blind, double-dummy • 320 adult patients with recurrent GH • Mean no. episodes in prior year FAM=9.0 VLT=9.1 • HSV serostatus HSV-2 only: FAM=30%, VLT=34% HSV-1 & HSV-2: FAM= 36%, VLT= 33% HSV-1 only: FAM=3%, VLT=3%	• FAM 250 mg BID (n = 159) • VLT 500 mg q AM (n = 161)	**Primary endpoint:** proportion of patients with clinically confirmed recurrence FAM=34%, VLT=28% P=NS **Secondary endpoints:** proportion of patients with virologically confirmed recurrence FAM=13%, VLT=6%, P=0.035 time to first clinical recurrence RR=1.17 P=NS time to first virologic recurrence RR=2.15, P=0.049 **Safety:** Headache most commonly reported, approximately 12% in each group. Two VLT patients experienced SAEs (hiatal hernia and chest pain) that were unrelated to treatment.
BID=Twice daily, FAM=Famciclovir, GH=Genital herpes, HSV=Herpes simplex virus, NS=Not significant, qAM=Every morning, RR=Relative risk, SAE=Serious adverse event, VLT=*Valtrex*		

8. UNAPPROVED USES

8.1 Use in pregnancy

valtrex and acyclovir in the third trimester of pregnancy

The comparative pharmacokinetics and safety profile of *Valtrex* (500 mg BID) and acyclovir (400 mg TID) were evaluated in 20 pregnant women at 36 weeks gestation with recurrent genital herpes.[58] Peak acyclovir plasma concentrations and daily AUC were significantly higher in *Valtrex* recipients versus acyclovir after the initial dose and at steady state. Acyclovir was concentrated in the amniotic fluid for both *Valtrex* and acyclovir recipients, but there was no evidence of preferential fetal drug accumulation. No patient experienced a genital herpes simplex virus (HSV) recurrence or asymptomatic shedding at delivery, as detected by PCR or culture and none of the patients required a cesarean section. Two patients receiving acyclovir reported nausea and headache and one patient receiving *Valtrex* reported headache. In addition, the pharmacokinetics of *Valtrex* 500 mg PO twice daily and acyclovir 400 mg PO three times daily in late pregnancy were similar to that observed in nonpregnant adults. Additional information can be found in Table 22.

Table 22. Use of *Valtrex* During the 3rd Trimester of Pregnancy[58]

Patient Population/ Study Design	Dosing Regimen	Results/Comments
• Prospective, randomized, double-blind • N=20 • 36-wks gestation • All women had + HSV-2 serology	• *Valtrex* 500 mg BID from wk 36-delivery (n=10) • Acyclovir 400 mg TID from wk 36-delivery (n=10) • Blood samples obtained after initial dose and at steady state (38 wk gestation) • Amniotic fluid samples collected during labor • Simultaneous cord blood and maternal plasma obtained at delivery	Pharmacokinetics*: Following First Dose at 36 wks • Cmax (mcg/mL): VLT 3.03 ACV 0.94 (P <0.0001) • Tmax (h): VLT 1.9 ACV 1.5 (P=0.48) • AUC (h·mcg/mL): VLT 17.8 ACV 7.7 (P<0.001) • $T_{1/2}$ (h): VLT 2.0 ACV 2.2 (P=0.47) Steady State at 38 wks • Cmax (mcg/mL): VLT 3.03 ACV 0.94 (P <0.001) • Tmax (h): VLT 1.9 ACV 1.5 (P=0.34) • AUC (h.mcg/mL): VLT 19.7 ACV 11.0 (P<0.009) • $T_{1/2}$ (h): VLT 2.6 ACV 3.2 (P=0.23) • Pharmacokinetics in late pregnancy similar to non-pregnant adults • No pt had a genital HSV recurrence or asymptomatic viral shedding at delivery (detected by culture or PCR) • No pt required C-section due to lesions at time of delivery • Mean maternal vein: plasma ratio=1.36 for ACV and 1.7 for VLT Safety profile: • Two patients receiving acyclovir reported nausea and headache, one patient receiving VLT Ireported headache. • No fetal drug accumulation, and no maternal clinical or laboratory drug toxicity with either ACV or VLT.

ACV=acyclovir; AUC=area under the curve; BID=twice daily; Cmax=peak concentration; HSV=herpes simplex virus; PCR=polymerase chain reaction; RGH=recurrent genital herpes; TID=three times daily; $T_{1/2}$=elimination half-life; Tmax=time to peak concentration; VLT=*Valtrex*

8.2 Use of Valtrex For Suppression Herpes Labialis (Cold Sores)

clinical information

Two randomized, double-blind, placebo-controlled, single-center studies evaluated the use of *Valtrex* for the suppression of herpes labialis among patients with a history of 4 or more recurrences in the previous year. [59] Patients were randomized to receive oral *Valtrex* 500 mg (n = 49) or placebo (n = 49) once daily for 4 months. Two patients from the *Valtrex* group and one patient from the placebo group either were lost to follow-up or withdrew prior to the first clinic visit, and were not included in the efficacy analysis.

Based on a pooled analysis of these two studies, more patients receiving *Valtrex* (60%) compared with placebo (38%) were lesion-free during the 4-month treatment period (*P*=0.041). The mean time to first recurrence was significantly longer in the *Valtrex* group (13.1 weeks) compared to the placebo group (9.6 weeks) (*P*=0.016). Adverse events reported during the 4-month treatment period were slightly lower in the *Valtrex* group (22 events, 33% of patients) compared to the placebo group (29 events, 39% of patients) with the most common adverse event in both groups being headache.

8.3 Use of Valtrex for Prevent of Cold Sores During Dental Procedures

Prevention of Cold Sores Associated with Dental Procedures

Miller et al[60] evaluated patients (≥ 12 years old) with a history of recurrent herpes labialis (≥1 episode/year and ≥1 episode in previous year) in a randomized, double-blind, placebo controlled study for the prevention of cold sore outbreaks associated with dental procedures (periodontal, restorative, endodontic, orthodontic, and oral surgery). Patients (n=125) were randomized to *Valtrex* 2 grams taken within one hour of the procedure and 2 grams taken the evening of the procedure followed by 1 gram twice daily on the next day, or matching placebo. Patients receiving placebo had more clinical lesions than patients receiving *Valtrex* (20.6% vs. 11.3%) during the one week observation period following treatment. In addition, there were more positive HSV-1 cultures (7.9% versus 1.6%) and more positive HSV-1 saliva specimens (7.9% versus 4.0%) in the placebo group versus the *Valtrex* group. Lastly, the mean time to cessation of pain was significantly less in patients receiving *Valtrex* versus placebo (3.2 vs. 6.2 days; P=0.006). However, there was no difference in the mean clinical lesion severity score between *Valtrex* and placebo. The most common adverse events for *Valtrex* vs. placebo were headache (14.5% vs. 4.8%), nausea (11.3% vs. 6.3%), diarrhea (1.6% vs. 3.2%), and sore throat/dry mouth (1.6% vs. 3.2%).

8.4 Use of Valtrex for Treatment of Herpes Gladiatorum

background

It is estimated that over 1 million athletes participate in wrestling each year.[61] Herpes gladiatorum, caused by herpes simplex virus type 1 (HSV-1), may occur in participants of contact sports, most often during wrestling or rugby. During any contact sport, team members may inadvertently transmit herpes through skin abrasions, which come in contact with existing herpetic lesions, such as herpes simplex labialis (cold sores). Signs and symptoms associated with herpes gladiatorum include vesicular herpetic eruptions, pain, fever, chills, myalgia, lethargy, sore throat, and headache. [62]

clinical information

<u>Suppression</u>

A single center, 2-phase trial of *Valtrex* was conducted between November 1996-March 1998 among 42 male high school and college wrestlers and their coaches in Minnesota (ages 15-31 years). [63] All wrestlers had a history of herpes gladiatorum based on clinical presentation or HSV-1 positive culture. The first phase of the study was double-blind and was conducted during the first half of wrestling season. The wrestlers received *Valtrex* 500 mg once daily or placebo during the course of the wrestling season. Phase II was an open-label study with all wrestlers receiving *Valtrex* 1 g once daily during the latter part of the wrestling season during tournament time. Herpetic outbreaks were treated with *Valtrex* 500 mg twice daily for 7 days, and infected wrestlers were subsequently removed from the study.

The previously described study was extended through the year 2000.[61]At that time, 116 wrestlers age 13- 30 years had been evaluated. Further information and results of both of these studies and are shown in Table 23.

Table 23. Use of *Valtrex* in Suppression of Herpes Gladiatorum

Ref	Study Design/ Patient Information	Dosage Regimen	Results/Comments
(63)	• 2 Phase Study • Double blind (Phase I); Open-label (Phase II) • Single Center • 42 Male Wrestlers (HS and College) with recurrent herpes gladiatorum • Hx of HG based on clinical presentation or HSV-1 positive culture • Ages: 15-31y	**Phase I**: VLT 500 mg QD or PBO QD **Phase II**: VLT 1 g QD (open-label)	**Phase I: Percent of Pts w/ Recurrence:** **VLT 500 mg (n=21) PBO (n=21)** **HG <2 y** 21% (3/14) 33% (5/15) **HG >2 y** 0% (0/7) 33% (2/6) **Phase II: Percent of Pts w/ Recurrence:** VLT 1 g (n=37) **HG <2 y** 8% (2/25) **HG >2 y** 0% (0/12) **Safety:** One pt d/c due to nausea. Adverse events were between VLT and PBO.
(61)	• 2 Phase Study • Phase I: Randomized, double-blind, Placebo controlled • Phase II: Open-label of wrestlers from Phase I • 116 wrestlers with herpes gladiatorum • Ages: 13-30 y	**Phase I:** VLT 1 g QD, VLT 500 mg QD, or PBO x 70 days **Phase II:** VLT 1 g QD x 51 days	**Phase I: Percent of Pts w/ Recurrence:** **VLT 500 mg VLT 1 g PBO** **HG <2 y** 21.4% (3/14) 3.7% (1/27) 20.5% (9/44) **HG >2 y** 11.8% (2/17) ---- 42.9% (6/14) **Phase II: Percent of Pts w/ Recurrence:** **VLT 1 g** **HG <2 y** 3.8% (3/80) **HG >2 y** 0% (0/30) **Safety:** Adverse events rates were similar between VLT and PBO groups.
BID=twice daily;d/c=discontinued; g=gram(s); h=hour(s); HG=herpes gladiatorum; hx=history; HS=high school; M=male; mg=milligrams; mo=month(s); PBO=placebo; Pt(s)=patients;PO=oral; QD=once daily; VLT=*Valtrex*; y=year(s)			

Treatment

A double-blind, placebo-controlled, prospective study was conducted in 29 wrestlers (ages 18-36) with at least a 2-year history of recurrent herpes gladiatorum. (64) Patients were randomized to receive placebo, *Valtrex* 500 mg BID, or *Valtrex* 1 gram daily for 7 days. The infected areas were swabbed daily for 14 days, and the samples were analyzed for HSV-1 or HSV-2 by PCR. The primary endpoint was determined as the last sample with measurable PCR detected. Of the 29 recruited participants, 20 experienced outbreaks (3 coaches and 17 active wrestlers) and began treatment within 24 hours of symptom onset. All of the PCR samples were positive for HSV-1. A 21% reduction in mean time until PCR viral clearance was observed with *Valtrex* 500 mg BID (6.43 days, 95% CI: 4.39-8.47) versus placebo (8.14 days, 95% CI: 5.9-10.38). Time to clinical clearance was also accelerated with *Valtrex* 500 mg BID (3.0 days, 95% CI: 0) versus placebo (5.43 days, 95% CI: 3.43-7.43).

8.5 Use of Valtrex for Prophylaxis of Herpes Gladiatorum

background

It is estimated that over 1 million athletes participate in wrestling each year (65). Herpes gladiatorum, caused by herpes simplex virus type 1 (HSV-1), may occur in participants of contact sports, most often during wrestling or rugby. During any contact sport, team members may inadvertently transmit herpes through skin abrasions, which come in contact with existing herpetic lesions, such as herpes simplex labialis (cold sores). Signs and symptoms associated with herpes gladiatorum include vesicular herpetic eruptions, pain, fever, chills, myalgia, lethargy, sore throat, and headache (62).

CLINICAL INFORMATION

A prospective evaluation of a 28-day wrestling camp in Minneapolis, MN from June to July 2003 followed 332 wrestlers for the occurrence of primary herpes gladiatorum [65]. Antiviral prophylaxis was offered to all camp participants, and was initiated in 243 wrestlers one week before entering camp. Eleven wrestlers had a history of recurrent herpes gladiatorum. Additionally, 28/94 (29.8%) with available blood samples had positive IgG anti-HSV-1 antibodies. Antiviral therapy was prescribed by the wrestler's personal physician, and of the 243 wrestlers on antiviral therapy, 231 took *Valtrex* 1 g once daily (physicians could also prescribe acyclovir or famciclovir). Three outbreaks occurred during the camp: one in a wrestler who did not receive antiviral prophylaxis and two in wrestlers receiving prophylaxis (one each, *Valtrex* and acyclovir). This correlated to an 87% reduction of herpes gladiatorum compared to camps prior to implementation of antiviral prophylaxis. No adverse events were reported.

8.6 Use of a One-Day Regimen with Valtrex for Genital Herpes

In an open-label, single-arm, pilot study, 90 patients (41 men, 49 women) received *Valtrex* (2 g BID) for episodic treatment of genital herpes.[66] Patients initiated therapy within 6 hours of the first prodromal symptoms or a genital lesion. Patients also were asked to keep a diary of daily symptoms for the total study period of 14 days. Patients with at least 4 episodes were included and patients who had received suppressive therapy in the past were included if they had at least six recurrences within the previous year and had not received antiviral therapy within seven days of the study drug. Patients who received suppressive therapy had to experience at least one outbreak following 3 months of discontinuation and 3 months prior to study entry. Patients were also asked to swab genital lesions daily for either viral culture or polymerase chain reaction (PCR) for 14 days until all signs and symptoms resolved to assess viral shedding.

The primary end point was episode duration (number of days between the earlier prodrome or initiation of therapy and complete resolution of all signs and symptoms). Secondary end points were lesion duration, duration of pain, duration of viral shedding, and percentage of aborted lesions (prodromal symptoms only).

A total of 90 patients were included in the intent-to-treat analysis (ITT) of whom, 77 patients developed lesions and 13 patients had only prodromal symptoms. A modified ITT was done that excluded patients with prodromal symptoms only (in the ITT population these patients were assigned a lesion duration of zero).

In the ITT analysis, the median number of recurrences in the year prior to study entry was seven. Patients initiated therapy with *Valtrex* within a median of 2 hours of the onset of symptoms, and the interval between taking the first dose and second dose was 11 hours. The median episode and lesion duration was 4 and 5 days in the ITT and ITT modified analyses respectively. Four patients who had lesions developed a recurrence after resolution of the initial lesion, and the median time from end of the first lesion to the beginning of the second lesion was 6.5 days.

Herpes simplex virus (HSV) HSV shedding data was analyzed from 478 swabs for culture and 1164 swabs for PCR collected over the 14-day study period. As shown in Table 24 below, HSV shedding was limited in patients who had prodrome only, and among the 77 patients who developed lesions, HSV was detected in 60 patients (78%) by PCR and 31 patients (42%) by viral culture. Additionally, among the 60 patients who had detectable HSV, 14 (23%) and 2 (3%) had a second and third shedding episode, respectively for a median of duration of shedding of 2 days.

The most common adverse events were headache (18%), nausea (7%), and fatigue (3%). One patient had a serious adverse event (worsening of depression) that was not considered to be drug related.

Table 24. Clinical and Virological Outcomes in Patients with Genital Herpes Recurrences[66]

Outcomes	N=90 (%)
Aborted episodes, number of patients (%) -Positive for HSV DNA, number of patients (%) -Positive for HSV culture, number of patients (%)	13 (14) 2 (15) 1 (8)
Lesional episodes, number of patients (%)* -Positive for HSV DNA, number of patients (%) -Positive for HSV culture, number of patients (%)†	77 (86) 60 (78) 31 (42)
Duration of lesion, median days (range)‡ -ITT population§ -Modified ITT population‖	4 (0-15) 5 (1-15)
Duration of episode, median days (range)‡ -ITT population§ -Modified ITT population‖	5 (1-15) 5 (1-15)
Duration of pain, median days (range)‡	3 (1-10)
Duration of HSV viral shedding¶, median days (range)‡ By HSV DNA PCR By culture By either PCR or culture	3 (1-13) 2 (1-4) 3 (1-13)
*The four episodes that occurred after the resolution of the first recurrence were excluded † Culture data for three patients were missing ‡ Median values expressed as the 50th percentile of the Kaplan-Meier estimate for survival. §Intent-to-treat, all patients who took study medication; subject with prodrome only were assigned a lesion duration of zero days. ‖All patients with lesional episodes ¶Includes first recurrences only	

8.7 Use of Valtrex for Herpes Zoster in Immunocompromised Patients

Published information

A randomized, double-blind, controlled trial evaluated two dosages (1 g or 2 g TID) of *Valtrex* for 7 days for the treatment of herpes zoster in 87 immunocompromised adult patients.[67] Immunocompromised patients with a clinical diagnosis herpes zoster had therapy initiated within 72 hours after the onset of rash and followed for 24 weeks. Patients were evaluated for zoster-associated-pain (ZAP), zoster-associated abnormal sensations (ZAAS), and herpes zoster complications. Patients were seen every other day for the first 2 weeks and then once weekly for 2 weeks, and then monthly for the remaining 5 months. Patients graded their average experience of pain since their last clinic visit on a scale of: no pain, just noticeable, mild, moderate, severe, or very severe.

The primary efficacy end point was time to complete resolution of ZAP. Secondary end points included: time to cessation of ZAAS (localized anesthesia, hyperesthesia, or pruritus), percentage of days (between days 1-28) with ZAP and/or ZAAS, and percentage of weeks (between 1-24) with ZAP and/or ZAAS.

Of the 87 patients who enrolled in the study, 63 (72%) completed the study; the most common reason for not completing the study was lost to follow-up (47% of patients). Patient demographics and clinical presentation at baseline (prodromal pain, prodromal pain severity, severity of zoster rash, rash onset before treatment) were similar between the two treatment arms. The immunocompromised status by disease state in the two treatment arms is summarized in Table 25 .

Table 25. Immunocompromised Status by Disease State of Study Participants

Patient type	*Valtrex* 1 g TID (n=45)	*Valtrex* 2 g TID (n=42)	Total (n=87)
Solid organ cancer	14 (31%)	17 (40%)	31 (35%)
HIV	10 (22%)	10 (23%)	20 (22%)
Autoimmune disease*	8 (17%)	7 (16%)	14 (16%)
Lymphoma	6 (13%)	8 (19%)	14 (16%)
Multiple myeloma	1 (2%)	0 (0%)	1 (1%)
COPD or emphysema*	3 (6%)	0 (0%)	3 (3%)
Solid organ transplant	2 (4%)	0 (0%)	2 (2%)
Cancer and autoimmune disease	1 (2%)	0 (0%)	1 (1%)
*patients received immunosuppressive therapy			

In a multivariate analysis of the time to cessation of ZAP, treatment with *Valtrex* 2 g TID was associated with a shorter duration of ZAP compared to 1 g TID, but this difference did not reach statistical significance (*P*=0.44). Of interest, compared to moderate rash at baseline, mild rash at baseline was associated with a shorter duration of ZAP (*P*=0.03).

In a multivariate analysis of secondary end points, time to cessation of ZAAS was similar in the two treatment arms. Mild rash at baseline was associated with a shorter duration of ZAAS (*P*=0.011). Patients who received *Valtrex* 1 g TID had a higher mean percentage of total days with ZAP (days 1-28) than those patients who received 2 g TID (85% vs. 76%, respectively). However, the percentage of days with ZAAS was higher for patients in the 2 g TID group versus the 1 g TID group (66% vs. 58%, respectively). Additional, results are summarized in Table 26 .

Table 26. Days Affected by Symptoms According to Treatment Group

Variable	*Valtrex* 1 g TID (n=45)	*Valtrex* 2 g TID (N=40)	P value
Percentage of days (1-28) with ZAP	85	76	0.122
Percentage of weeks (1-24) with ZAP	56	45	0.092
Percentage of days (1-28) with ZAAS	58	66	0.45
Percentage of weeks with (1-24) ZAAS	44	46	0.655
Time from treatment initiation to full crusting Patients, no. Mean (median) time, days	 40 10.9 (8)	 38 10.1 (8)	 0.765 -
Patients with ≥1 zoster-associated complications no (%)	2 (4)	3 (7)	-

The median ratings of pain was similar in the two treatment groups. A total of 13% of patients in each group reported (1 g TID and 2 g TID) severe or very severe painTable 27.

Table 27. Median Patient Reported ZAP

Severity of Pain	*Valtrex* 1 g TID (n=45) no. (%)	*Valtrex* 2 g TID (n=45) no. (%)
Just noticeable	8 (18%)	6 (15%)
Mild	15 (33%)	15 (38%)
Moderate	16 (36%)	14 (35%)
Severe	5 (11%)	4 (10%)
Very severe	1 (2%)	1 (3%)

Adverse events were collected for the first 10 days of the study, and then, only serious adverse events (SAE) possibly attributable to study drug were reported. A total of 22 (49%) of patients who received *Valtrex* 1 g TID and 25 (60%) of patients who received 2 g *Valtrex*TID had reported an adverse event.

Drug-related adverse events were reported in 6 patients in each treatment arm (13% and 14% of patients in the 1 g TID and 2 g treatment arms, respectively) The most common drug-related adverse events were headache, pain, nausea, vomiting, and constipation. SAEs were reported in 19 patients (6 in the *Valtrex* 1 g group and 12 in the 2 g group). Three SAEs led to study withdrawal.

There were significant changes from baseline in chemistry (hyponatremia and elevated transaminases) hematology (anemia, thrombocytosis, and high white blood cell count and/or neutrophil count) laboratory values were observed during the study. These changes were considered to be unrelated study medication.

9. ECONOMIC IMPACT MODEL

9.1 Currently, an economic impact model for is not available *Valtrex*.

Enclosure: Prescribing Information for *Valtrex*

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Appendix

Table 15. Valtrex for the Reduction in Risk of Heterosexual Transmission of Genital HSV-2 [4]

Patient Population	Study Design/Drug Regimen	Results
• Immunocompetent, heterosexual, monogamous couples discordant for HSV-2 Ab • Source partner must be seropositive for HSV-2 w/hx of ≤9 episodes/yr • Susceptible partners included 488 women and 996 men • HSV-1 serostatus in susceptible partner: 78% female and 64% male were HSV-1 seropositive • Source partner had median 7 year history of genital herpes • Median duration of couple's relationship at entry was 2 years	• Randomized, multicenter, double-blind, placebo controlled • Compared VLT and placebo for reduction in risk of transmission of HSV-2 GH • Source partner randomized in a 1:1 ratio to receive VLT or placebo for 8 months • Susceptible partner monitored for clinical and subclinical (serological) acquisition of HSV during the 8-mo study period • Primary Endpoint: symptomatic HSV-2 acquisition • Secondary Endpoints: HSV-2 seroconversion and overall HSV-2 acquisition	**Susceptible Partners Acquiring Symptomatic GH*** • VLT = 0.5% (4/743) • PBO = 2.2% (16/741); *P*=0.011 RR, 95% CI: 0.25 (0.08, 0.74) = 75% reduction in risk at end of study period **Time to Symptomatic Acquisition of Genital HSV-2*** • Significantly shorter in PBO group compared to VLT group (*P*=0.008) HR, 95% CI: 0.25 (0.08, 0.75) = avg. 75% reduction in risk at any time during study **Overall Acquisition of Genital HSV-2†** • VLT = 1.9% (14/743) • PBO =3.6% (27/741); *P*=0.054 RR, 95% CI: 0.52 (0.27, 0.97) = 48% reduction in risk at end of study period **Time to Overall Acquisition of Genital HSV-2†** • Significantly shorter in PBO group compared to VLT group (*P*=0.039) HR, 95% CI: 0.52 (0.27, 0.99) = avg. 48% reduction in risk at any time during study **HSV-2 Seroconversion‡** • VLT = 1.6% (12/743) • PBO =3.2% (22/741); *P*=0.060

* Defined as symptomatic first episode of genital HSV-2 in susceptible partner; confirmed by culture, PCR, or HSV-2 seroconversion
† Defined as laboratory confirmed symptomatic first episode genital HSV-2 and/or seroconversion in susceptible partner
‡ Defined as HSV-2 seroconversion in susceptible partner
Ab=antibody, cx=culture, d=days, PBO=placebo, PO=orally, pt=patient, q=every, QD=once daily, Sx=symptoms, Tx=treatment, VLT=*Valtrex*

Patient Population	Study Design/Drug Regimen	Results
	• Couples offered condoms and counseled on safer sex throughout study • 89 source partners participated in a 60-day substudy to assess viral shedding **Drug Regimen** • VLT 500mg PO QD (n=743) or Placebo PO QD (n=741) for 8 months	RR, 95% CI: 0.50 (0.25, 0.99) = 50% reduction in risk • The benefits of VLT were in addition to those provided by safer sex counseling • No statistical evidence that efficacy of VLT varied across subgroups studied (i.e., no evidence that VLT was more/less effective due to gender, HSV-1 status, condom use, number of sexual contacts, or time since first diagnosis). However, the small number of events limits statistical power to detect difference in efficacy • Significantly more source partners receiving suppressive therapy with VLT stayed recurrence free compared to PBO (P<0.001) **Total Viral Shedding (symptomatic and/or asymptomatic)** • VLT = 2.9%, PBO = 10.8% days; P<0.001 • 73% reduction in mean total shedding rate
		Asymptomatic Viral Shedding (shedding w/o lesions) • VLT = 2.8% days, PBO = 7.8% days; P<0.001 • 64% reduction in mean asymptomatic shedding rate **Adverse Events** • Incidence and severity were similar for treatment groups. Commonly reported AEs were headache, nasopharyngitis, and upper respiratory tract infection.

* Defined as symptomatic first episode of genital HSV-2 in susceptible partner; confirmed by culture, PCR, or HSV-2 seroconversion
† Defined as laboratory confirmed symptomatic first episode genital HSV-2 and/or seroconversion in susceptible partner
‡ Defined as HSV-2 seroconversion in susceptible partner
Ab=antibody, cx=culture, d=days, PBO=placebo, PO=orally, pt=patient, q=every, QD=once daily, Sx=symptoms, Tx=treatment, VLT=*Valtrex*